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FOREWORD

THE Annual Meeting of the American Academy of Pediatrics which normally would have been held in November this year was omitted in order to help the railroad transportation problem brought about by the war and the shortage of physicians in civil life. It is estimated that a meeting would take over 2,000 physicians' days from practice.

In place of the meeting the Editorial Board of the JOURNAL has made this issue a special Annual Meeting number.

It contains the customary presidential address of the retiring president and the papers of the two recipients of the annual E. Mead Johnson Awards. The first award was given to Dr. Hattie E. Alexander, New York, N. Y., for her work in the treatment of Hemophilus influenzae meningitis, and the second, to Dr. Philip Levine, Newark, N. J., for his work on the Rh factor.

In addition, a symposium on the general subject of the blood is presented which was arranged by the Editors to take the place of the usual panel discussion at the meeting.

Finally, the Minutes of the Executive Board meeting held November 6 in Chicago, together with the annual committee reports, are included.

PRESIDENTIAL ADDRESS

BORDEN S. VEEDER
ST. LOUIS, MO.

THE war has brought many problems to the Academy, but I feel after two years that our Academy problems are not in any way major ones. A year ago members of your Executive Board recognized that large medical meetings were neither advisable nor justified and reported this at the last Annual Meeting. While we miss our national and regional meetings, the work of the Academy is so organized that its activities are far from being suspended. Emphasis was placed at the meetings of the state chairmen last November that the work of the Academy for an indefinite period would depend more and more on our state chairmen and that Academy activities would be successful to the extent to which the state chairmen accepted their responsibilities. Many, I am glad to say, have risen to the occasion, and the longer the war lasts, more and more will our Academy work depend on the activity of the regional and state groups.

Pediatries, we must realize, is not a medical specialty closely related to military medical efforts. It is rather a field of medical practice related to the home front. In total warfare, as war is today, it becomes a distinct part of the war effort, and thus the pediatrician has an important medical contribution to make. Despite the fact that there is no particular place for the pediatrician as a pediatrician with the Armed Forces, 310 Fellows of the Academy, nearly 22 per cent of our membership, are in service. This is a high figure when we consider that only between 3 and 4 per cent of our membership are under 35 years of age and 35 per cent are in the 35- to 45-year age group. There are, of course, many more pediatricians than this in service, as over 2,100 pediatricians have been certified by the American Board of Pediatrics. A very large percentage of the 600 odd certified by the Board and eligible to Academy membership, but who are not members, are in service. To these must be added the large group of men who have finished their pediatric hospital training in the last two years. Of the men in service, a few have been assigned to contagious disease and sanitary service, and a very few are actually practicing pediatrics in Army and Navy camps. Letters from all over the world have crossed my desk from pediatricians doing a wide variety of medical military duties. Even if pediatrics is a specialty that does not fit directly into the medical picture of military organization, there has been ample demonstration of the spirit of the physician whose medical work is with children, and we can look with pride on our associates who have entered service.

Whether or not it would have been better in the long run to have planned for the trained children's physicians to have remained on duty

in civil life, time alone will tell. This is not a question for us to consider or argue about when the first necessity is winning the war. The important thing is that we have been honored by the Fellows who have gone into service, and we are very proud of them.

REGION V

One of the most important events in the development of the Academy since its founding was the action taken at the last Annual Meeting creating Region V, Central and South America. During the past year this action has been implemented and groups have been formed and admitted to the Academy from Argentina, Brazil, Chile, Cuba, Ecuador, Guatemala, Honduras, Mexico, Peru, and Venezuela. All told, nearly one hundred of our pediatric colleagues from the countries south of the United States have been admitted to the Academy in Region V, and a number of the groups have been of sufficient size to be organized with a chairman and secretary. Due to present conditions it has been impossible for us to greet them personally, and so we must be content to welcome them and congratulate both them and ourselves on making our Academy of Pediatrics a truly representative body of the pediatricians of the Americas.

An increase in the number of student fellowships has permitted a large number of the younger men from Central and South America to spend a year in our pediatric clinics. At present, thirteen of the Fellowships are filled, with six students from Mexico, two each from Peru and Venezuela, and one each from Brazil, Colombia, and Chile. They are distributed in twelve pediatric clinics: Harvard, Yale, Pennsylvania, Johns Hopkins, Cincinnati, Michigan, Chicago, Illinois, Iowa, Minnesota, and California Universities, and the Children's Memorial Hospital in Chicago. There can be no doubt that as these younger pediatricians, whom we are learning to know personally under the Academy fellowships, return to their home countries and become part of their local Academy groups, our relationship with the Fellows of Region V will become much closer. Most certainly in postwar days the time element of travel will be annihilated, and geographic distance will not even be the factor it was among the regional groups in our own country when the Academy was founded.

SOME CURRENT PROBLEMS

Food for Infants and Children.—Food rationing has not created the problems in providing adequate nourishment for infants and children that were anticipated. The Academy has been alert on the question of milk and processed infant foods, and, except for temporary difficulties in distribution, no real hardships have developed. Rationing in itself has been a good thing in a reverse way in that it has made millions of American women food conscious and, of necessity, concerned with matters of diet. Through one mechanism or another, hundreds of thousands of women have received instruction in food values and food needs who, in all probability, would not otherwise have been interested in nutrition. There is obvious danger that as the war progresses and after it has

ended the necessity of further sharing our food will lead to certain shortages such as dairy products.

One curious situation is that with all our governmental insistence on the maintenance of the health of children, grants to dependent children of men in service and the establishment of federally financed day nurseries and child health centers, the taxing authorities have steadily decreased the income tax exemption for dependent children until today the exemption is below the cost of maintenance of a child. It is a sort of a robbing of Peter to pay Paul situation which simply does not make sense. It might be in line for the Academy to take some action on this matter and state our attitude to the taxing authorities of the Government.

THE CARE OF CHILDREN IN FOREIGN COUNTRIES

Early in the year our colleagues of the British Pediatric Society addressed themselves to us on the question of the postwar care of children in countries devastated by our enemies. It is obvious that this is not a problem to be met by a group of physicians. On the other hand there is a huge medical problem involved and your officers felt that the members of the Academy might be of help by furnishing technical advice and by obtaining the best available personnel when and if needed. It consequently offered the services of the Academy in any way that it might be desired to the Red Cross and to the Office of Foreign Relief and Rehabilitation, which just at that time was created in the State Department under ex-Governor Lehman of New York. A short time later the Medical Service of the Office set up a small subcommittee on the medical care of the child, to which several members of the Academy were appointed.

We know that conditions in the occupied countries are almost beyond belief and will continue to become worse the longer the war lasts. The urgent problems to be faced are starvation, epidemic disease, and the special problem of maternity and infancy. There are two phases to be considered: first, the care of the population of the countries now being gradually occupied by the allied armies, and, second, the problem that will come when the war ends. Although those in the Office of Relief and Rehabilitation were planning on immediate action, the military authorities consider that relief at present only can be carried out directly under their supervision and as a part of their function. An initial period of two months has recently been extended to six months, under which relief will be at the hands of the military authorities. First of all must come food and sanitation, and only later can the special services be built up. Within the last month the Office of Foreign Relief and Rehabilitation has been abolished and its functions taken over by another agency. The only action that we of the Academy can take in this matter is to continue to offer our services in any way they may be desired. Some who have had a vast experience with relief in foreign countries feel that no effort will be of value unless sanitary and health measures are

built up by the physicians and health workers of these countries themselves with our aid and that the transplanting of foreign personnel to do the detailed work is of little value. As a matter of fact, there is ample technical personnel in the Army itself for all types of medical work that may be needed, and the chances are that there will be little or no demand for physicians from civilian life for relief purposes. We must remember that this problem of relief and rehabilitation is not simply an American problem but one that involves the United Nations.

THE JOURNAL OF PEDIATRICS

One of the most noticeable effects of the war so far as medical matters are concerned has been in the appearance of our medical journals. It has not been so much the paper shortage which has contributed to the steady shrinkage in the size as it has been the decrease in the number of manuscripts submitted for publication. Some feel we should look upon this as a gain rather than a loss. Our hospital and teaching staffs have been reduced in numbers and are teaching the year around. Of necessity, research has been curtailed and little time is left for the preparation of papers. The Editorial Board of the JOURNAL is determined it will not lower standards in accepting manuscripts, and hence we must look forward to a reduction in the size of the JOURNAL as the war continues. Perhaps our greatest loss is the disappearance of the Panel and Round Table Discussions which automatically disappeared with the discontinuance of our meetings. So far the JOURNAL has fared better than most, but the effect of the war will be more noticeable this coming year.

FINANCE

With the discontinuance of meetings and remission of Academy dues to Fellows in Service, the Academy income has decreased and will continue to decrease. The Executive Committee may have to reduce expenses but should not to an extent which would interfere with important Academy functions. The Academy has a reserve fund which it has accumulated over the past ten years, and this should be drawn upon if necessary. The reserve fund was not created as an endowment fund but as a reserve to meet emergency conditions and most certainly the conditions have developed which the fund was created to meet.

POSTWAR POSTGRADUATE EDUCATION

One of the immediate tasks before the members of the Academy is to prepare for postwar postgraduate education in pediatrics. Many letters have come across my desk from men in service who have been practicing pediatrics for a number of years and from graduates who have recently or only partially finished their resident training before entering service. Many in one way or another express a fear of forgetting their training in pediatrics and of becoming out of touch. Two things seem to me to be necessary: First, a definite plan to take back

into our hospitals as residents the better, at least, of those men whose training has been interrupted by their being called to service. This is something we owe them. Second, the planning of brief refresher courses of a few weeks or a month's duration. Some fifteen years ago our Committee on Medical Education was extremely active. The work of this Committee gradually decreased due to the formation of the American Board of Pediatrics. I feel it most important that our Committee on Medical Education be activated to make plans along the lines I have indicated. Postgraduate refresher courses should be arranged to be implemented when our pediatric colleagues begin to be discharged from military service. These courses should be limited to pediatricians so that they cannot be used as a stepping stone to specialization as they were fifteen to twenty years ago before standards of graduate education were established by the Board.

MEDICAL EDUCATION AND PRACTICE

A presidential address today before a medical organization would be avoiding the matter with which we are all most concerned if it failed to contain at least a reference to certain trends in medical education and practice. The difficulty lies in making such a discussion brief enough to be included in a presidential address.

In recent years many physicians have realized that medical technical progress has led to the need for changes in the mechanisms of medical care and practice. I know of no one who has been able to say just what these changes should be, but basically they are concerned with a more equitable distribution of the increased cost of good medical care which has been brought about by the scientific developments in diagnosis and in the treatment of the sick, so that good medical care is available to every one. Many, including myself and other Academy presidents as individuals and in no way related to the Academy, have hoped to see these inevitable changes brought about in an evolutionary way, retaining all that is good in the old but adding mechanisms and methods of practice that would meet changed and changing conditions. We had hoped that new ideas would be met with the same tolerance and scientific attitude that the medical profession has met new ideas and methods in therapeutics, knowing full well that only methods which stood the test of time would make a permanent place for themselves.

Unfortunately, as we all realize today, there has been a vociferous reactionary group in control of much of our medical organization and our medical press who have used every method to retain a medical status quo in a world that has been changing in every other field and activity. Everyone, even the conservative who was tolerant, who expressed any progressive idea or who thought medicine must meet changing conditions was labeled a dangerous radical who should be read out of the medical profession. Emotion rather than reason became dominant and colored most of the discussion that has taken place. The pediatricians as a

group, I am glad to be able to say and proud to be one of them, in all this turmoil during the last twenty years have stood as the most progressive group in medicine and they have, as all will admit, done the most in reducing morbidity and mortality. I need only cite the action of the pediatric group as far back as 1922 in regard to the Shepherd-Towner Bill to illustrate my point.

As a result of the failure of the medical profession to meet changing conditions in the last twenty-five years, due in no small part to rather stupid, selfish leadership, we are confronted today, as a result of the war, by certain revolutionary changes in medicine which are of great potential danger to the welfare of medicine, both to the practitioner and to the patient. Due to the position in which we have been placed, we are unfortunately poorly situated to oppose what is bad in the proposed changes, as the medical profession is regarded as a reactionary body in a progressive world. This is an unfair judgment in many ways and one particularly untrue of the pediatrician, but nevertheless one that exists.

The two revolutionary measures are the one accomplished: the taking over of the control of medical education by the Federal Government, and, the second, the revolutionary proposals of the Wagner-Murray-Dingell bill. The dangerous element that exists in both is the lowering of standards of medical education and practice. Nothing of value to the public will be gained by changing the economics of medicine unless our high standards of practice are maintained.

While in theory the taking over of our educational institutions is a temporary military measure, it is now proposed that educational training for the returned soldier must be provided for, which will mean continuance of governmental control and direction of education which I cannot but feel will lower admission standards and the character of medical education. I have still to find the teacher who does not feel that the work of our medical students has deteriorated since they have been militarized.

As to the revolutionary Wagner-Murray-Dingell bill I am not so concerned, for it is so expansive that from an economic standpoint it is impractical in its present form. It does, however, express the trend of thinking of what will seemingly be the dominant postwar political thought. Here, again, perhaps the most dangerous element in the bill is the failure to concern itself with and to provide for and safeguard the maintenance of high medical standards. We must remember that the Beveridge plan, concerning which there has been so much discussion, is premised on a postwar return to prewar economic levels in Great Britain.

We can be certain that there will be postwar changes in medical practice. There are a number of forces that will bring this about. First among these will be a continuing pressure of certain social, political, and labor groups which have been so active in recent years. Second, there will be a vast extension of the Veterans' program due to the addition of millions of ex-soldiers to the veterans groups, which have been so

powerful politically in the past twenty years. A third factor will come from the younger physicians themselves, those men who are now subsidized by the Government to study medicine and who by the thousands are now on salaries in the military services. We can be quite certain that a large percentage of this group of young physicians will never be content to enter the practice of medicine on an individual competitive basis as medicine has largely been practiced in the past. The one thing to be regretted is that with all that has been staring us in the face for over two decades, the medical profession has put itself into a position where, as an organized group, it is not trusted and so will have little to say, although any real solution to the problems of medical economics must have the support of the members of the medical profession if good medical care is to be provided.

Of more immediate concern to us today is the emergency maternity and child health measures now administered by the Children's Bureau to provide medical care for the dependents of certain ranks in service. The original purpose was to provide good medical care for those who were unable to obtain such care because of financial reasons, and with this purpose no one can or did quarrel. The medical profession was in sympathy with the purpose and plan. First, however, the criterion of need was removed and the fact that the Government would pay for such service was widely publicized through notices from the Children's Bureau sent out with allottments and to the men in service through military channels. This led immediately to the need for increased appropriations by Congress and this, in turn, to the plan taking on distinct political aspects. The standards established by the Children's Bureau were partially eliminated by Congress with the result that from a medical standpoint there is not the slightest assurance that good medical care, the very purpose of the plan, is being or will be given. The net result then is a monetary subsidy to the wives and children of soldiers of certain ranks for maternal and child health care, whether such a subsidy is or is not needed. Further, the Children's Bureau set up certain arbitrary administrative regulations, which are not in the bill, that have aroused the resentment of the obstetricians and pediatricians, as they imply that they are not to be trusted. The result in brief is that a Government bureau, by its regulations, has imposed an arbitrary fee system upon the physicians of America in which they have had no voice and control. Certainly this is bureaucracy at its worst. The matter will come up at the meeting of the Executive Committee of the Academy and I can assure the many Fellows who have communicated with me in regard to the matter that we in the Academy will do everything possible to bring about certain changes in the picture.

I appreciate very deeply the honor which the Academy has conferred upon me by asking me to act as its president. I cannot help but recall

the meeting of some twenty men in a hotel room in Montreal in the spring of 1930, only thirteen years ago, when it was decided to form the Academy to meet the needs of our rapidly growing medical specialty. What the Academy has developed into and its influence on the medical care of the children of America in these past thirteen years is, in retrospect, almost miraculous. Those of us who were present at that meeting had hopes and aspirations, but no one could possibly have visualized the place the Academy would take in such a short space of time. The time has been reached when the pioneer leadership not only of necessity but rightly must be passed over to an entire new group of men. As one of the "old guard," I feel that this new leadership which has been gradually developing will carry on and lead the Academy to even greater achievements than it has seen in the past decade. To have been privileged to have had a small part in the formation and the early development of the Academy is one of the finest things that has happened to me personally in my medical life and is one of the few things I look back upon as being worth many many times the effort that it entailed.

EXPERIMENTAL INVESTIGATIONS AS A BASIS FOR TREATMENT OF TYPE B HEMOPHILUS INFLUENZAE MENINGITIS IN INFANTS AND CHILDREN

HATTIE E. ALEXANDER, M.D., AND GRACE LEIDY
NEW YORK, N. Y.

IT IS, perhaps, not going too far to assert that a combination of sulfonamide with type-specific antibody has been proved to be the treatment of choice in cases of influenzal meningitis in infants and children. Nonetheless, publications asserting the sufficiency of the various sulfonamides when used alone continue to appear. These reports fail both to present sufficient data and to include enough cases to warrant conclusions. However, the fact that chemotherapy alone does succeed from time to time indicates a need to examine the matter more closely and to determine, if possible, the circumstances under which the sulfonamides can be relied upon and when the combined treatment must be used. This paper will attempt to supply additional experimental data on the relative importance of the sulfonamides and serum and information on the relative merits of the several sulfonamides which are in everyday use, and to offer a simple, rapid method for evaluating the sulfonamide sensitivity of strains isolated from patients judged suitable for a trial period of chemotherapy alone.

The experience upon which our preference for the combined treatment is based has been summarized in a previous report.[1] This experience includes three types of evidence: First, a study of the biologic features of *H. influenzae* type b; second, the results of treatment of influenzal meningitis in infants and young children; third, the outcome of certain laboratory investigations which will be described and which it is the purpose of this report to supplement.

Concerning the first point, there is reason to believe that type-specific antibody plays an important role in recovery from infection. It has been shown that the satisfactory quantitative relationship between antigen and antibody which is the aim of serum therapy can be attained practically in three steps:

1. By the use of a therapeutic product which has been assayed by a quantitative chemical method.[2] The analytical procedure on which this method depends measures the protective element by quantitating the anticarbohydrate antibody.[3]

From the Department of Pediatrics, College of Physicians and Surgeons, Columbia University.

The work reported in this communication was supported by grants from the Commonwealth Fund.

2. By the application of laboratory criteria for evaluation of the severity of infection. Chief among these criteria is the concentration of reducing substance in the spinal fluid. A quantitative determination of the spinal fluid dextrose prior to treatment has been recommended as the most satisfactory index for general use.[4] When the quantity present is below 10 mg. per 100 c.c., the prognosis is poor and all experience indicates that antibody administration is essential to recovery. Prolonged coma with signs suggestive of encephalitis also points to a severe process.

3. By check of the sufficiency of a given dose of serum through examining the patient's blood for satisfactory excess of free antibody. The capacity of the patient's serum to produce capsular swelling when diluted 1:10 has been adopted as the desirable excess. The reaction of the patient to the intracutaneous injection of the specific carbohydrate also provides this information.

The results of treatment of influenzal meningitis in infants and children by the combined method have been gratifying. Of seventy-five patients who received one of the sulfonamides along with type-specific rabbit serum, fifty-seven, that is 76 per cent, recovered. All recoveries were complete except for mild reduction of vision in one patient who during the acute stage of the disease had shown bilateral retinal hemorrhages. Of these patients who survived, forty-three, or 75 per cent, were under 3 years of age and twenty-eight, approximately one-half, were under 2 years of age. Eighteen received rabbit antibody only after prolonged periods of unsuccessful treatment elsewhere with various sulfonamides alone or combined with horse serum. In Table I is listed the duration of meningitis prior to the administration of rabbit serum and also the outcome of treatment for this group of patients treated for a long time with other agents.

Examination of the data relating to these patients points to certain conclusions:

1. Each of the sulfonamides used exerted a significant influence on the course of the infection.

TABLE I

PATIENTS TREATED IN OTHER HOSPITALS WITH OTHER FORMS OF THERAPY FOR LONG PERIODS PRIOR TO THE USE OF TYPE B RABBIT ANTIBODY

DURATION OF MENINGITIS BEFORE ADMINISTRATION OF RABBIT SERUM (WK.)	RESULTS OF TREATMENT		
	RECOVERY	DEATH	TOTAL
2	2	3	5
3	3	2	5
4	4	1	5
5	1	0	1
6	1	0	1
7	1	0	1
Total	12	6	18

2. Type-specific antibody appeared to be an essential element of treatment for many patients with *H. influenzae* meningitis. The number of the total who require it remains to be defined.

3. Eventual recovery following the administration of rabbit antibody was conditioned by the degree to which the infection had previously been held in check. The severity of infection in these patients as judged by the criteria just described is not known.

From the foregoing it is permissible to infer that the capacity of the sulfonamide compounds to effect complete recovery from *H. influenzae* infections is influenced by two factors: First, the infection must be relatively mild. Mildness is not a customary attribute of infections caused by *H. influenzae* type b, for they are characteristically severe. Second, the drug must be started early in the course of the infection. It is believed that only under such circumstances will sufficient time be afforded to the patient to produce through his own powers sufficient antibody to overcome the disease. The capacity of patients, under favorable and possibly exceptional circumstances, to develop type-specific antibodies is demonstrated by the fact that agglutinins against *H. influenzae* have been demonstrated in two patients who recovered from meningitis after treatment with sulfonamide alone and in one with type b *H. influenzae* pneumonia which responded promptly to sulfadiazine.

Experimental investigations dealing with the relation of therapeutic agents to survival and pathogenicity of *H. influenzae* organisms provide additional data on which to base a rational program of clinical practice. Three general lines of inquiry have been followed:

1. Study of the relative efficiency of serum and sulfadiazine alone and combined in protecting mice against type b *H. influenzae* infections.

2. Relative minimal effective concentration of the commonly used sulfonamide compounds in vitro.

3. Comparison of the minimal mouse-protective dose of these drugs.

MATERIALS AND METHODS

Mouse Protection Test.—The mouse protection tests used throughout these experiments have been so thoroughly standardized that they possess a high degree of reproducibility. Organisms are suspended in mucin in order to render them lethal in small numbers in control animals, thus eliminating the toxic factor. Miller first used this method of enhancement of virulence in mouse virulence tests with meningococcus.[5] Fothergill and co-workers[6] applied the principle to *H. influenzae* virulence tests in mice.

Culture: Cultures grown from the first spinal fluid withdrawn at the Babies Hospital were dried and sealed under vacuum by a method devised by Brown.[7] Organisms so preserved show no significant loss of virulence for an indefinite period of years. A new specimen of dried

culture was planted in Levinthal broth[8] within forty-eight hours of the time each test was performed. A Levinthal agar plate was seeded with 0.3 c.c. of an eighteen-hour Levinthal broth culture, and after five and one-half to six hours incubation the growth was washed off with plain nutrient broth and the density adjusted to 3.5 cm. by the Gates turbidimeter. Using the latter as the standard suspension, dilutions were made in mucin at multiples of 10 from 10^{-1} to 10^{-9}. The dose of organisms indicated in the experiments was suspended in 1 c.c. of mucin and introduced into the peritoneal cavity within one hour following the injection of the serum and two to three hours following administration of the sulfonamides. The minimal number of organisms causing death in 50 per cent of the mice, or the minimal lethal dose, was determined for all cultures each time they were used in testing a protective agent. In all instances twenty or fewer organisms were sufficient to kill 50 per cent of the control mice inoculated. The protective power of all agents tested is expressed in terms of the number of minimal lethal doses, against which at least 50 per cent of the mice were protected.

Mucin: Seven grams of finely powdered mucin* were dissolved in 100 c.c. of distilled water by grinding in a mortar with a pestle, the water being added to the powder in small amounts after intervals of grinding to obtain a smooth paste. The suspension was sterilized by autoclaving at ten pounds for fifteen minutes. Large particles were removed by centrifuging for five minutes at the slowest centrifuge speed. The supernatant fluid was then adjusted to pH 7.2 with normal sodium hydroxide and 1 per cent dextrose added.

Mice: White Swiss male mice were used throughout all experiments. Except when indicated otherwise, the weight range was 13 to 15 Gm. All mice were weighed on the day of the test.

Drug Administration: All the sulfonamides were administered before as well as after the injection of the organisms. The finely powdered drugs were suspended in 10 per cent gum acacia and introduced through the esophagus directly into the stomach by means of a blunted 18 gauge needle attached to a 1 c.c. syringe. The doses used are indicated in the experiments described.

In Vitro Method for Comparing the Antibacterial Action of Sulfonamides.—Three different media have been found to support the growth of *H. influenzae* to such a degree that an inoculum of less than ten organisms will produce an easily perceptible turbidity within eighteen hours: Levinthal broth, Dingle's broth,[9] and MacLeod's liver medium.[10] The last has been selected because MacLeod's test for inhibitors[11] showed it to contain less of these factors.

The same strain of type b *H. influenzae* has been used throughout the experiments which compare the minimal effective concentration of the

*Lots No. 43457 and No. 51556, type 1701W, Wilson Laboratories.

sulfonamides. In an effort to determine the influence of age of cultures, six-hour and sixteen-hour cultures have been used as the inoculum for the in vitro tests. In the experiments using six-hour cultures the growth from Levinthal agar was washed off with 5 c.c. of MacLeod's liver medium and diluted until the turbidity by the Gates turbidimeter read 3.5 cm. The colony count of this suspension varied between 1.5 and 2.0 billion. The sixteen-hour cultures were prepared by inoculating 0.2 c.c. of a six-hour Levinthal broth culture into 15 c.c. of liver medium in a 250 c.c. flask. The turbidity at sixteen hours varied from 3.2 to 3.5 cm. by the Gates turbidimeter and the colony counts from 100 million to 320 million. Comparison with the colony count on the six-hour culture suspensions of approximately the same turbidity shows that not more than one-fifth of the organisms contributing to turbidity of sixteen-hour cultures are alive. From this point on, the six- and sixteen-hour cultures were handled in the same way.

Serial dilutions of both the six-hour and sixteen-hour cultures, 10^{-1} through 10^{-9}, were made in MacLeod's liver medium. From this series, which served as the control, dilutions of 10 through 10^{-2} through 10^{-6} were made in liver medium containing four different concentrations of each drug to be tested. The range of concentrations of the individual sulfonamides was selected in such a way that equal effective ionic strengths could be compared. The data of Fox and Rose,[12] by which they had shown that the concentration of the ionized form of a sulfonamide determines its activity against *Escherichia coli*, formed the basis for the relative concentrations of the solutions of sulfonamides used in these experiments and listed in Table II.

TABLE II

RANGE OF DRUG CONCENTRATIONS USED FOR DETERMINING M.E.C.* OF SULFONAMIDES IN VITRO

DRUG	CONCENTRATIONS USED (MG. PER 100 C.C.)			
Sulfanilamide	360	36	18.0	3.6
Sulfapyridine	50	5	2.5	.5
Sulfathiazole	10	1	.5	.1
Sulfamerazine	10	1	.5	.1
Sulfadiazine	10	1	.5	.1

*M.E.C., Minimal effective concentration.

EXPERIMENTAL RESULTS

Examination of the Efficiency of Sulfadiazine and Rabbit Antibody Singly and Combined in Protecting Mice Against Lethal type b. H. influenzae Meningitis.—Preliminary results of this investigation were reported in 1942.[13] Subsequently, Pittman[14] published similar observations. A summary of all of our experimental evidence on this question has been reported recently.[1] The essential details will be presented in this paper.

TABLE III

SAMPLE OF A MOUSE TEST COMPARING THE PROTECTIVE VALUES OF SULFADIAZINE AND SERUM SINGLY AND COMBINED

PROTECTIVE SUBSTANCE	DOSAGE OF ORGANISMS (EXPRESSED IN M.L.D.)*															
	10^7		10^6		10^5		10^4		10^3		10^2		10		1	
	D§	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Sulfadiazine†			10	0	6	4	2	8								
Serum‡			9	1	6	4	3	7								
Sulfadiazine and serum	8	2	2	8	1	9										
Control											8	2	7	3	5	5

*Colony count of standard suspension, 1,600,000,000 per c.c.

†Dose, 2 Gm. per kilogram first day; 0.6 Gm. per kilogram daily on second and third days.

‡Dose, 0.6 c.c. of 1:100 dilution = 0.011 mg. antibody nitrogen.

§D, Deaths; S, survivals.

Serum in the amounts listed for each experiment was given intraperitoneally within one hour prior to injection of the mucin suspension of *H. influenzae*. The dose of sulfadiazine was kept constant throughout: 18 mg. before and 9 mg. following the infection on the first day; 9 mg. on the second day, and 9 mg. on the third day. On this schedule the blood level of the mice at the time of injection was about 20 mg. per cent. Twenty hours following the second dose of drug, given after the infection, the blood level varied between 38 and 49 mg. per cent. The administration of such a large quantity represented an attempt to determine the maximal protection with sulfadiazine.

On five different occasions experiments were performed in which sulfadiazine and serum singly and combined were tested at the same time for their capacity to protect mice against the same lethal suspension of *H. influenzae* type b. A representative test is shown in Table III. The minimal lethal dose in this test was one to two organisms, since 10^{-9} dilution of the standard (colony count 1,600,000,000) caused death of 50 per cent of the animals. Ten minimal lethal doses would therefore

TABLE IV

SUMMARY OF FIVE EXPERIMENTS COMPARING THE MOUSE PROTECTIVE VALUES OF SERUM AND SULFADIAZINE SINGLY AND COMBINED

PROTECTIVE AGENTS	DEGREE OF PROTECTION EXPRESSED IN M.L.D.				
	TEST 1	TEST 2	TEST 3	TEST 4	TEST 5
Sulfadiazine*	10,000	10,000	10,000	10,000	10,000
Serum†	10,000	10,000	100,000	10,000	10,000
Antibody N dose per mouse	.097 mg.	.009 mg.	.012 mg.	.012 mg.	.011 mg.
Sulfadiazine and serum	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000
Total number of mice	65	65	115	120	120
Number of mice per dose of organisms	5	5	10	10	10

*Powdered sulfadiazine was suspended in 10 per cent gum acacia and given perorally 27 mg. the first day, 9 mg. the second day, and 9 mg. the third day.

†Sera were used in 0.6 c.c. volume of 1:100 dilution except in Test 1, in which 1:10 dilution was used.

represent sixteen organisms. It is seen from Table III that sulfadiazine protected eight out of ten mice against 10,000 minimal lethal doses or 16,000 organisms. Serum alone protected seven out of ten against the same inoculum. When the inoculum was increased to 160,000 organisms (100,000 or 10^5 minimal lethal dose), these agents given singly failed to protect 50 per cent of the mice, and when the dose was further increased to 10^6 minimal lethal dose or 1,600,000 organisms, there was absence of protection. The two agents combined, on the other hand, protected eight out of the ten mice inoculated with 1,600,000 organisms.

In Table IV is tabulated the degree of protection obtained with sulfadiazine and rabbit antiserum, singly and in combination, in each of five experiments. The maximal protection afforded by each agent with regularity was 10,000 minimal lethal doses. Larger quantities of antibody failed to increase the protection with sufficient consistency to be convincing. The combination, on the other hand, protected against 1,000,000 minimal lethal doses with striking regularity.

It is apparent that a significant difference has not been demonstrated between the average protection afforded by sulfadiazine administered for three days and serum given intraperitoneally in one dose when each is used alone.

Study of the Correlation of Inhibitory Capacity of the Sulfonamides in the Test Tube and in the Mouse.—

Results of In Vitro Tests.—Four different concentrations of a given drug were inoculated with varying numbers of type b *H. influenzae* listed in the tables. After twenty-four and forty-eight hours' incubation periods, turbidities were read in the Klett-Summerson filter photometer and the tubes showing no visible clouding were recorded.

TABLE V

IN VITRO TEST FOR DETERMINING MINIMAL EFFECTIVE CONCENTRATION OF SULFANILAMIDE AGAINST SIXTEEN-HOUR BROTH CULTURE

	READINGS OF FILTER PHOTOMETER AFTER 24 AND 48 HOURS' INCUBATION							
Drug concentrations (mg. per 100 c.c.)								
360	46	45	24	30	16	18	14*	15*
36	53	57	35	40	15	30	7*	6*
18	50	57	37	46	22	41	5*	4*
3.6	51	65	45	53	35	44	27	51
Control 0.0	59	72	66	67	59	72	58	70
Time of incubation	24 hr.	48 hr.	24 hr.	48 hr.	24 hr.	48 hr.	24 hr.	48 hr.
Inoculum (number of organisms per cubic centimeter	2,400,000		240,000		24,000		240	

*No visible turbidity.

Table V is a representative example of an individual in vitro test in which the minimal effective concentration of sulfanilamide against a sixteen-hour culture is investigated. In Table VI are listed the re-

TABLE VI

IN VITRO TEST FOR DETERMINING MINIMAL EFFECTIVE CONCENTRATION OF SULFAMERAZINE AGAINST SIXTEEN-HOUR BROTH CULTURE

	READINGS OF FILTER PHOTOMETER AFTER 24 AND 48 HOURS' INCUBATION							
Drug concentrations (mg. per 100 c.c.)								
10.0	35	37	17	15	8	7	8*	7*
1.0	40	41	19	33	11	8	7*	5*
0.5	47	50	23	33	8	40	8*	5*
0.1			48	53	51	53	42	48
0.05	50	57	55	60	55	61	55	58
Control 0.00	55	67	55	64	52	52	52	53
Time of incubation	24 hr.	48 hr.	24 hr.	48 hr.	24 hr.	48 hr.	24 hr.	48 hr.
Inoculum (number of organisms per cubic centimeter	1,000,000		100,000		10,000		100	

*No visible turbidity.

sults of an identical test, with sulfamerazine as the experimental inhibitory agent.

The results are all expressed in the readings taken directly from the Klett-Summerson filter photometer. The asterisk is used to indicate when the eye could not detect turbidity. Kohn and Harris[15] and Kirby and Rantz[16] have reported on the use of readings of turbidity by a filter photometer in making quantitative estimations of inhibition by sulfonamides.

The criteria to be satisfied in determining the minimal effective concentration have not yet been generally agreed upon. Certain points seem clear. It is the inhibitory action rather than the killing effect which is of prime interest. Rose and Fox[17] have shown that for some unexplained reason organisms continue to reproduce in media containing effective concentrations of sulfonamides over a period necessary for approximately six generations. Therefore, if one wishes to use as simple a criterion as possible, as, for example, the failure of growth based on absence of visible clouding in forty-eight hours, one must select an inoculum so small that six reproductive cycles during the so-called lag phase will not be sufficient to produce a turbidity.

In Table V it is seen that an inoculum of 240 organisms was satisfactory for this purpose. Other experiments show that a range from 100 to 1,700 organisms is satisfactory for determining minimal effective concentrations according to this criterion. In Table V the minimal effective concentration of sulfanilamide by this standard is 18 mg. per cent. In Table VI the minimal effective concentration of sulfamerazine is shown to be 0.5 mg. per 100 c.c. Quantitative determinations of growth by means of a filter photometer offer a simple time-saving method for testing the susceptibility of an inoculum of any size to varying concentrations of sulfonamides. Kohn and Harris[15] are of the opinion that any concentration of drug which inhibits the growth

of the organisms to such a degree that the turbidity produced is only one-half that of the control, or less, is an effective one. When an inoculum of 10,000 to 20,000 organisms is selected for application of this second criterion, it is seen in Tables V and VI that 18 mg. of sulfanilamide and 0.5 mg. of sulfamerazine per 100 c.c. represent effective inhibitory concentrations when readings are made after twenty-four hours' incubation.

Sulfapyridine, sulfathiazole, and sulfadiazine were also examined for their minimal effective concentrations according to these two standards:

1. Concentration necessary to prevent visible growth in forty-eight hours following an inoculum of 100 to 1,700 organisms.

2. Concentration necessary to reduce the turbidity of the twenty-four-hour growth from an inoculum of 10,000 to 20,000 organisms to, at most, one-half that of the control.

TABLE VII

COMPARISON OF RELATIVE INHIBITORY EFFECT OF SEVERAL SULFONAMIDE COMPOUNDS TESTED BY THEIR EFFECT ON GROWTH OF H. INFLUENZAE TYPE B IN VITRO

PROTECTIVE DRUG	CONCENTRATIONS TESTED (MG. PER 100 C.C.)	MINIMAL EFFECTIVE CONCENTRATION (MG. PER 100 C.C.)	
		FOR PREVENTION OF VISIBLE GROWTH FROM 100 TO 1,700 ORGANISMS FOR 48 HR.	FOR INHIBITION OF 10 TO 20,000 ORGANISMS TO HALF TURBIDITY OF CONTROL IN 24 HR.
Sulfanilamide	360, 36, 18, 3.6		
6-hr. culture		18.0	18.0
18-hr. culture		18.0	18.0
Sulfapyridine	50, 5, 2.5, 0.5		
6-hr. culture		2.5	2.5
18-hr. culture		2.5	2.5
Sulfathiazole	10, 1.0, 0.5, 0.1		
6-hr. culture		0.5	0.5
18-hr. culture		0.1	0.5
Sulfadiazine	10, 1.0, 0.5, 0.1		
6-hr. culture		0.5	0.5
18-hr. culture		0.5	0.5
Sulfamerazine	10, 1.0, 0.5, 0.1		
6-hr. culture		0.5	0.5
18-hr. culture		0.5	0.5

Table VII lists the minimal effective concentrations for all five drugs according to each of these criteria, both when the inoculum is a six-hour culture and when it is a sixteen-hour culture. It is seen that the minimal effective concentration of sulfanilamide is 18 mg. per 100 c.c. or thirty-six times as great as that of sulfathiazole, sulfadiazine, and sulfamerazine, which are effective in concentrations of about 0.5 mg. per 100 c.c. A concentration of sulfapyridine of 2.5 mg. per 100 c.c. is required to produce comparable inhibition. These relative minimal effective concentrations are in general agreement with the results of

TABLE VIII

COMPARISON OF THE MOUSE PROTECTIVE VALUES OF VARYING LEVELS OF THREE SULFONAMIDES (MICE WEIGHING FROM 12 TO 15 GM.)*

PROTECTIVE AGENTS (MG.)		RESULTS OF FOUR EXPERIMENTS (PROTECTION EXPRESSED IN M.L.D.)							
DAY 1	DAY 2	1†		2		3		4	
Sulfanilamide									
4		(0)‡	1,000						
8	8	(0)	1,000	(0)	100	(0)	100	(0)	100
15	8	(0)	1,000	(0)	100	(0)	100	(0)	100
Sulfapyridine									
3	3	(0)	1,000	(0)	100	(0)	100	(0)	100
6	6	(0)	10,000	(0)	100	(+)§	100	(+)	100
12	12	(0)	10,000	(0)	100				
18	9							(0)	100
Sulfadiazine									
2	2	(+)	1,000	(+)	1,000	(+)	1,000	(0)	1,000
4	4	(+)	10,000	(+)	1,000	(+)	1,000	(+)	1,000
8	8	(+)	10,000	(0)	10,000				
Total number of mice		120		165		165		170	

*In Experiments 1, 2, and 4 the majority of mice weighed 13 Gm. and in Experiment 3, 12 Gm.

†Drug administered on first day only.

‡(0). No protection against the number of M.L.D. listed. The number of M.L.D. listed represents the minimal dosage of organisms used.

§(+). Protection against the number of M.L.D. listed. The number of M.L.D. listed represents the maximal dose of organisms against which protection was obtained.

Fox and Rose,[12] who used *E. coli* as the test organism. The differences in the minimal effective concentrations of the different drugs for *H. influenzae* bear a close relationship to their degree of ionization at pH 7.0.

Minimal Dose of the Sulfonamides Effective in Mouse Protection Tests: In Table VIII are compared the quantities of sulfapyridine and sulfadiazine necessary to protect mice weighing 12 to 15 Gm. against varying inocula of *H. influenzae* type b. The majority of mice used in Experiments 1, 2 and 4 weighed 13 Gm. Most of those used in Experiment 3 weighed 12 Gm. During the period over which these experiments were performed it appeared necessary to select mice of this weight range in order to obtain reproducible results with the mucin then available.

When sulfanilamide was given in dosage above 8 mg., the first day's dose was split. This was done because mice will not tolerate larger doses of sulfanilamide at one time. All the sulfapyridine doses were split in an attempt to distribute the intake of the drug so as to produce a blood concentration curve comparable with that which resulted from sulfadiazine administration.

The results of four separate experiments are listed in Table VIII. Both sulfanilamide and sulfapyridine in doses which aimed to maintain comparable blood concentrations failed to protect mice of this weight range, 12 to 15 Gm., against 100 minimal lethal doses or ap-

TABLE IX

COMPARISON OF THE MINIMAL DOSES OF SULFANILAMIDE, SULFAPYRIDINE, AND SULFADIAZINE NECESSARY FOR PROTECTION AGAINST THE NUMBER OF M.L.D. OF TYPE B H. INFLUENZAE INDICATED (MICE WEIGHING FROM 14 TO 17 GM.)

INTERVAL AFTER DRUG INTAKE	SULFANILAMIDE (MG.*)		SULFAPYRIDINE (MG.*)					SULFADIAZINE (MG.*)				
	8	15	3	6	8	16	32	0.4	0.8	2.0	4.0	8.0
Blood concentration (mg./100 c.c. [1 to 2 hr.])	28-35				19-20							
Blood concentration (mg./100 c.c. [3 to 4 hr.])	6-7	13-21			19-20					12-15		
Blood concentration (mg./100 c.c. [20 hr.])	6-14	16-28	4-7.5	5-8	7-8	15-18	13-18	1.6	1.5-2.5	4-7	5-8	5-15
Protection (M.L.D.)												
Experiment 1	+100†	+100†	+100†	+1,000†		+10,000†				+1,000†	+10,000†	+10,000†
Experiment 2					+1,000‡	+1,000‡	+1,000‡	+1,000‡	+1,000‡	+1,000‡		

*All drugs were administered for two days, according to the schedule described in Table VIII.

†Protection against the number of M.L.D. listed. The number of M.L.D. listed represents the maximal dose of organisms against which protection was obtained.

‡Protection against the number of M.L.D. listed.

TABLE X

COMPARISON OF MINIMAL DOSES OF SULFATHIAZOLE AND SULFAMERAZINE NECESSARY FOR PROTECTION AGAINST 1,000 M.L.D. OF H. INFLUENZAE TYPE B (MICE WEIGHING FROM 14 TO 17 GM.)

INTERVAL AFTER DRUG INTAKE	SULFATHIAZOLE (MG.*)			SULFAMERAZINE (MG.*)					
	0.4	0.8	2.0	0.1	0.2	0.5	2.0	4.0	8.0
Blood concentration (mg./100 c.c. [3 hr.])	2.0	5-6	9.5	2.5-3	4-5	8-11	16	27	35
Blood concentration (mg./100 c.c. [20 hr.])	<0.8	<0.8	<0.8	<0.8	<0.8	5.5	7-10	9-13	11-17
Protection (M.L.D.)									
Experiment 1	(0) 1,000†	(0) 1,000	(0) 1,000				(+) 1,000‡	(+) 1,000	(+) 1,000
Experiment 2				(0) 1,000	(0) 1,000	(0) 1,000			

*Both drugs administered in the daily dose listed for 2 days.

†(0), No protection against the number of M.L.D. listed. The number of M.L.D. listed represents the minimal dosage of organisms used.

‡(+), Protection against the number of M.L.D. listed. The number of M.L.D. listed represents the maximal dose of organisms against which protection was obtained.

proximately 15,000 organisms. Sulfadiazine, on the other hand, protected against 1,000 to 10,000 minimal lethal doses or 150,000 to 1,500,000 organisms.

The present lot of mucin permits a high degree of reproducibility when the weight of the mice is kept within the range of 14 to 17 Gm. Table IX lists the minimal dosage of sulfanilamide, sulfapyridine, and sulfadiazine necessary for protection of mice in this weight range. The schedules of drug administration used are identical with those for experiments in Table VIII. The blood concentration of the mice receiving different doses of the three drugs is tabulated for three intervals following drug administration. Certain facts stand out. There is a great variation in blood levels of mice on the same dosage of the same drug. Sulfanilamide and sulfapyridine must be administered in larger and more frequent dosage than sulfadiazine to obtain comparable blood concentration curves. When the dose of sulfanilamide was increased to the maximum compatible with lack of drug toxicity, protection against 100 minimal lethal doses was the highest obtained. A comparison of the minimal doses of sulfapyridine and sulfadiazine necessary for protection against 1,000 minimal lethal doses shows that a dose between 3 and 6 mg. of sulfapyridine is required, whereas 0.4 mg. of sulfadiazine is sufficient. When blood concentrations are compared, it is clear that sulfadiazine is effective in lower concentration.

Table X shows the results obtained when it was attempted to determine the minimal effective dose of sulfathiazole and sulfamerazine. It is clear from the blood level results that sulfathiazole must be used in larger and probably more frequent dosage than sulfamerazine or sulfadiazine to afford comparable protection. No protection was obtained in the quantity used against 1,000 minimal lethal doses. However, twenty hours after the administration, the blood levels were too low to read. Sulfamerazine in 0.5 mg. dose did produce what would have been a satisfactory level for sulfadiazine and yet no protection was afforded. This evidence suggests that sulfadiazine is a more efficient agent for protecting mice against type b *H. influenzae* infections. More work must be done to answer this question.

DISCUSSION

It is clear from the results that all the sulfonamides exert a significant inhibitory effect against *H. influenzae,* both in the test tube and in infected mice. A fairly extensive experience with mouse protection tests for comparison of sulfanilamide, sulfapyridine, and sulfadiazine leaves no doubt that the last is the drug of choice among these three. The difference was most striking in younger mice. Even in older mice it required twenty times more sulfanilamide to provide protection against 100 minimal lethal doses than is required of sulfadiazine for protection against 1,000 minimal lethal doses. Likewise, the minimal protective dose of sulfapyridine against 1,000 minimal lethal doses was fifteen times that

of sulfadiazine. Part of this difference is due to requirement of a higher and more frequent dose of sulfapyridine and sulfanilamide in proportion, in order to maintain blood levels comparable to those obtained by a given dose of sulfadiazine. Nevertheless, comparison of protection on the basis of blood concentrations shows that sulfadiazine is effective in much lower concentration than either sulfapyridine or sulfanilamide. Our experience in comparing the mouse protective value of sulfamerazine and sulfathiazole with these drugs is too limited to be of significance, but suggests that they too will be required in larger dosage than sulfadiazine. Rapidity of excretion is probably an important influencing factor in the case of sulfathiazole, as is shown in Table X, but a given dose of sulfamerazine produces a higher blood level than an equal dose of sulfadiazine. All of this evidence points to the fact that the drug of choice at present, as judged by the capacity to protect mice, is sulfadiazine.

The in vitro test results likewise show that sulfadiazine is vastly superior to sulfanilamide and definitely superior to sulpyridine, as judged by minimal effective concentration values. Sulfathiazole and sulfamerazine possess an inhibitory capacity approximately equal to that of sulfadiazine.

It seems clear that when one limits the comparison to the three drugs with which we have most experience—sulfanilamide, sulfapyridine, and sulfadiazine—there is a direct correlation between the protective value in mouse infections and the inhibitory capacity in the test tube. Sulfadiazine is the most effective drug by both methods. In mice, 0.4 mg., yielding a blood concentration of 1.6 mg. per 100 c.c. after twenty hours, is effective in protecting against 1,000 minimal lethal doses. The minimal effective concentration in the test tube was also small, 0.5 mg. per 100 c.c. Sulfapyridine is the next most effective of the three by both standards, and sulfanilamide is the poorest drug. The dose of the latter drug required to protect mice against 1,000 minimal lethal doses would be so high that death would result from the toxicity of the drug. The great difference in the minimal effective concentration of sulfanilamide and sulfadiazine is obvious (Table VII). The dependence of this difference on the relatively poor ionization of sulfanilamide at pH 7.0 is implied on the basis of the work of Fox and Rose[12] with *E. coli.*

Sulfadiazine is limited in its power to protect mice when the inoculum exceeds a certain maximum, no matter how high the concentration of the blood is raised. This maximum appears to be at 10,000 minimal lethal doses. Serum alone, likewise, usually fails to protect when the inoculum exceeds this range. When these two agents are combined, the mice regularly withstand 1,000,000 minimal lethal doses.

This synergistic effect of the two agents appears to be essential in the treatment of severe type b *H. influenzae* meningitis in infants and children. When the infection is judged mild, as indicated by a concentration of dextrose in the spinal fluid of 40 mg. or more per 100 c.c.,

and when the clinical features are in keeping with this, the use of sulfadiazine alone is justified initially. Our experience suggests that the simple in vitro tests may be of value in determining the susceptibility of a given strain to sulfadiazine. If these tests indicate satisfactory inhibition, as judged by the minimal effective concentration values listed in Table VII, it is believed that the drug alone may be continued without risk, provided clinical improvement ensues and provided the spinal fluid shows the infection to be under control, with cultures sterile forty-eight hours after the start of chemotherapy. Two points deserve emphasis:

1. A longer period of sulfonamide appears to be necessary, if recovery is to be complete on sulfadiazine alone, than is required when rabbit antibody is used in addition. When both agents have been combined it has been our policy to discontinue sulfadiazine one week after sterilization of the spinal fluid, provided the chemical and cellular constituents of the fluid are in the normal range and the clinical improvement parallels the laboratory results. If sulfadiazine is used alone, this period should probably be extended to two weeks.

2. The initial improvement seen so frequently following the use of the sulfonamides can be very misleading. The patient may seem to be better, judged either clinically or by spinal fluid changes. The cells show a striking decrease, the sugar rises, and the organisms are not seen in stained smears; but the use of satisfactory culture media[4] yields growth of the organisms and thus demonstrates that the infection remains active. We have seen many examples of such circumstances.

SUMMARY

Experimental results demonstrate that there is a close correlation between the mouse protective capacity of sulfonamides and their degree of inhibition in the test tube against type b *H. influenzae*. Sulfadiazine is vastly superior to sulfanilamide and definitely more effective than sulfapyridine.

A simple in vitro test is described for estimating the susceptibility of a given strain to sulfadiazine within forty-eight hours of isolation.

Sulfadiazine and type-specific rabbit antibody, when used singly, have been shown to possess approximately equal protective value against lethal type b *H. influenzae* mouse infections. However, regardless of the dose administered they fail to protect regularly when the inoculum exceeds 10,000 minimal lethal doses. Mice treated with both agents together quite regularly survive following the injection of 1,000,000 minimal lethal doses.

It seems quite clear that in the treatment of patients with influenzal meningitis the risk of failure is reduced to a minimum by the use of both serum and sulfadiazine. However, if the infection is judged mild by

clinical and laboratory criteria, initial treatment with chemotherapy alone is justified, provided the recommended precautions and guides are used and provided the strain shows average susceptibility to sulfadiazine.

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THE PATHOGENESIS OF ERYTHROBLASTOSIS FETALIS

A Review

Philip Levine, M.D.
Newark, N. J.

IT IS now established that erythroblastosis fetalis is caused by isoimmunization of the mother by a dominant hereditary blood factor in the fetus; most frequently, the Rh (rhesus) factor. This intrauterine hemolytic disease of the fetus and the newborn infant occurs under highly specific conditions, determined by the presence or absence of the Rh factor in the parents. In more than 90 per cent of the cases the father's blood contains the Rh factor (Rh+), the mother's blood lacks the factor (Rh–), while the fetal blood must possess it (RH+). The two essential steps in the pathogenesis of erythroblastosis fetalis are (1) the response of the Rh– mother to the foreign Rh+ fetal blood by production of anti-Rh agglutinins and (2) the continuous passage of maternal anti-Rh agglutinins through the placenta to react with and hemolyze the susceptible fetal Rh+ blood. While this theory provides the source of the long-suspected intrauterine hemolytic process, it must, at the same time, offer an explanation for the mechanism of isoimmunization of the mother. In other words, how does the fetal red blood cell—a formed element—enter the maternal circulation in sufficient quantity to stimulate the mother to produce anti-Rh agglutinins? That maternal antibodies find their way into the fetal circulation is an indisputable fact.

In this paper it is proposed to elaborate on the pathogenesis of erythroblastosis fetalis and to summarize the findings reported to date. As a preliminary it seems desirable to review the pertinent serologic facts since the findings on erythroblastosis fetalis were made exclusively by means of serologic procedures, which may not be entirely familiar to the pediatrician.

The term isoimmunization in contrast to heteroimmunization implies immunization with the same species. Isoimmunization in man by means of red blood cells cannot occur unless there exist individual differences of human blood. An outstanding example of such differences are the four blood groups, determined by the varying distribution of two agglutinable factors, A and B. Since the antibodies specific for these factors are present in normal human serum, these antibodies

From the Division of Laboratories of the Newark Beth Israel Hospital.
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are termed normal isoagglutinins. It is not generally appreciated that there exist in human blood numerous other blood factors, most prominent of which are the subgroups of A (A_1 and A_2) and the properties M, N, and P. In contrast to the Rh factor, these factors are not antigenic in man; that is, they are incapable of inducing isoimmunization and hence they play no role in the selection of donors for transfusions. Thus, the antibodies for M and N must be produced by heteroimmunization; that is, injection of rabbits with selected human blood.

Isoimmunization is readily induced in numerous species of animals by means of repeated blood transfusions. The reactions of the isoantibodies thus produced indicate the existence of numerous blood factors antigenic within the species. Until recently isoimmunization in man following repeated blood transfusions has been demonstrated but very rarely, although it has been suspected because of the greater frequency of intragroup transfusion reactions in the patients in this group. In other words, atypical, presumably immune, agglutinins could not readily be demonstrated in these cases. It is now established that the Rh factor is antigenic in man, so that by virtue of its capacity to induce isoimmunization, it has become clinically important in the prevention of intragroup transfusion accidents and in the pathogenesis of erythroblastosis fetalis. One of the most unexpected findings from these recent studies is the capacity of the Rh factor to induce isoimmunization not only by means of repeated blood transfusions but also during the course of pregnancy. In the latter case the Rh– mother is immunized by Rh+ fetal blood, while in the former instance the Rh– patients may be immunized by numerous transfusions of Rh+ blood. It is significant that the very first transfusion of mothers of infants with erythroblastosis fetalis with Rh+ blood may result in violent hemolytic reactions ending in severe or fatal anuria.

The Rh Factor.—In 1937 Levine and Stetson[1] studied the serologic properties of the blood of a mother who delivered a macerated fetus. Because of excessive bleeding this patient (group O) was transfused with the blood of her husband (group O). This, the first transfusion, was followed by a severe chill and pains in the legs and head. This patient had moderately active atypical agglutinins in her serum which agglutinated 80 per cent of all group O bloods. Subsequently, six uneventful transfusions were given with selected compatible donors. The agglutinin gradually became weaker at the end of two months, and at the end of one year it disappeared completely. The main feature of this case was the origin of this atypical agglutinin, and the authors suggested that it was produced by transplacental isoimmunization. In other words, the mother was immunized by a particular blood factor which was present in the fetus and in the father. Obviously, this factor could not be present in the mother's blood.

While it was evident that the factor was independent of other known blood properties, its identity or relationship to other blood properties

could not be established until human anti-Rh sera became available to Levine and Katzin (December, 1940). It could then be shown that this patient was Rh–, her husband was Rh+, and the atypical agglutinin was anti-Rh in specificity.* Furthermore, all her compatible donors were Rh–.

In January, 1940, Landsteiner and Wiener[3] studied the specificity of an immune serum produced in rabbits (later in guinea pigs) by injections of the blood of *Macacus rhesus*. This serum, after suitable absorption, was found to agglutinate 85 per cent of all human bloods. These bloods were termed Rh+ by Landsteiner and Wiener, and the 15 per cent inactive bloods, Rh–. Accordingly, Landsteiner and Wiener demonstrated the factor in rhesus blood which is related to the agglutinable property previously observed by Levine and Stetson.[1]

No clinical importance could be attached to this experimental observation until Wiener and Peters showed that Rh– individuals may be immunized by repeated transfusions with Rh+ blood, and further transfusions with this blood resulted in severe hemolytic reactions. These observations were soon confirmed by several authors.

The Early Observations on Isoimmunization by Pregnancy and Fetal Death.—The observation of a high incidence of transfusion reactions in obstetric patients with the very first transfusion led to the description of the pathogenesis of erythroblastosis fetalis.[4] Apparently these patients must have been immunized by a particular blood factor in fetal blood at some time during the course of the pregnancy.† In each of these early cases, evidence of isoimmunization was based on the demonstration of atypical agglutinins. There was already evidence that in the majority of these cases, the mother was Rh– and the atypical agglutinin was anti-Rh in specificity.

The second fact of significance was the high incidence of neonatal or fetal death (miscarriage or stillbirth) in this group of transfusion accidents. Accordingly, it was suggested that the two phenomena, isoimmunization of the Rh– mother by the Rh factor of fetal blood and fetal death, were correlated.[4]

Since the cause of the fetal or neonatal death in some of these instances could be assigned to erythroblastosis fetalis diagnosed on the basis of clinical and pathologic findings, it was suggested that the action of maternal anti-Rh agglutinins on Rh+ fetal blood might be the source of the long-suspected intrauterine hemolytic process.[5]

In order to investigate this question further, a statistical study was undertaken to determine the incidence of the Rh factor in a selected population of mothers of erythroblastotic infants. Such a study was

*That the Rh factor was involved in this case was previously suspected by Wiener and Peters.[3]

†Wiener and Peters[3] indicated that the explanation of Levine and Stetson held also for other cases reported in the literature dealing with transfusion reactions at the first transfusion.

feasible because large quantities of potent anti-Rh sera produced by several of these mothers were available. As will be shown below, the Rh factor is a complex antigen so that there are at least three common varieties of anti-Rh sera.

Technique of Agglutination Tests.—

A. *Test Tubes or Slides:* The criteria of differentiation of Rh+ and Rh− individuals depend upon the presence or absence of agglutination. Like all hemagglutination reactions, the tests may be carried out either in test tubes or on slides. Since many anti-Rh sera give stronger reactions at 37° C. than at room temperature,[6] it is preferable to use test tubes. In practice it will be necessary to determine the presence or absence of the Rh factor not only in the blood of the mother, but also in that of the infant and the father. Accordingly, the only practical method is to resort to the use of small test tubes (75 by 10 or 12 mm.), so that several tests may be carried out at the same time.

B. *The Blood Suspension:* A cell suspension may be prepared either from a few drops of finger blood diluted in saline or from the clot. Since the agglutinability of red blood cells is best preserved in the presence of serum, sufficient blood should be drawn and allowed to clot. Stored in the icebox, suitable cell suspensions could readily be obtained from the seven- to fourteen-day-old clot.

Although it is not essential, I prefer to wash the blood suspension once and to resuspend the sedimented cells in saline to make a 2 per cent suspension. For a standard comparison the turbidity of the resuspended cells should correspond to that resulting from the addition of one drop of whole blood to 4 c.c. of saline.

C. *The Test:* One or more drops of anti-Rh serum* are mixed in small test tubes with 2 drops of the washed suspension. The tubes are shaken and placed in a water bath at 37° C. for one hour. The mixtures should be shaken several times during the course of the hour.

D. *Reading:* It cannot be emphasized too much that it is important to examine the appearance of the sediment in the mixtures. A round, firm sediment indicates the absence of agglutination, while an irregular, loose sediment indicates gross agglutination. At the end of the incubation period, the quality of the sediment should be observed. The test tubes are then numbered for identification and centrifuged gently for one minute (400 to 500 r.p.m.). After replacing the tubes in the rack, the quality of the sediment is again noted before each tube is gently shaken. The intensity of the agglutination is recorded as ±, +, +±, etc. The readings are facilitated by the use of a small hand lens. Those mixtures in which no gross agglutination is visible are examined microscopically (low magnification) by withdrawing some of the mixture onto a slide with the aid of a glass rod. Bloods showing no agglutination are Rh−.

*For the inhibition of anti-A and anti-B agglutins in anti-Rh sera by the group-specific substances of Witebsky, see page 662.

Detection of Human Anti-Rh Sera.—Two drops of the serum to be tested for the presence of anti-Rh agglutinins are added to each of ten small test tubes and each tube receives two drops of washed cell suspensions of ten different group O bloods. It is essential to include representative bloods as indicated in Table II. As a rule, there will be difficulty only in obtaining a blood Rh′ because of its low incidence. The tests are incubated for one hour at 37° C. and readings are made as indicated above. (Reference to standardization of anti-Rh sera suitable for diagnostic purposes will be found under that heading later in this paper.)

The Varieties of Human Anti-Rh Sera.—The early observations revealed that the Rh factor is a mosaic composed of several antigenic substances.[7-10] This is based on the fact that not all human anti-Rh sera, in contrast to anti-A or anti-B sera, give parallel reactions. Based on the incidence of plus and minus reactions, the vast majority of human anti-Rh sera fall into one of the three types indicated in Table I.

TABLE I

RESULTS OF PARALLEL TESTS ON 334 RANDOM BLOODS OF ALL GROUPS*

ANTI-Rh SERUM FROM PATIENT	Rh+ (%)	Rh− (%)
E. B.	87	13
M. F.	85	15
M. S.	73	27

*From Levine and associates.

These reactions may be classified so that there are four types of bloods as indicated in Table II. The terminology for the agglutinins and for the subvarieties of the Rh antigen is that suggested by Wiener and Landsteiner.[11]

TABLE II

AGGLUTINATION REACTIONS OF THREE ANTI-RH SERA WITH 334 RANDOM BLOODS OF ALL GROUPS

TERMINOLOGY OF WIENER AND LANDSTEINER	INCIDENCE OF TYPE (%)	MRS. M. F. ANTI-Rh	MRS. M. S. ANTI-Rh_1	MRS. E. B. ANTI-Rh′
Rh_1	71	+	+	+
Rh_2	14	+	−	+
Rh′	2	−	+	+
Rh−	13	−	−	−
Incidence of + reactions (%)		85	73	87
Incidence of − reactions (%)		15	27	13

The sera were obtained from mothers of erythroblastotic infants. These tests were carried out in April, May, and June, 1941.

It will be observed that bloods containing the factors Rh_2 and Rh′ are qualitatively different, as indicated by the cross-specific reactions in a manner analogous to the reactions of group A and B bloods with their respective agglutinins. Accordingly, it could be suspected that anti-Rh and anti-Rh_1 sera contain qualitatively different agglutinins,

both of which are present in the anti-Rh′ serum.[12] This could be confirmed in absorption tests so that the anti-Rh′ serum could be converted either into an anti-Rh or anti-Rh_1 serum.

Only individuals who are Rh– (13 per cent) or Rh′ (2 per cent) may be immunized by the factors Rh_1 or Rh_2. In the vast majority of the cases the mother of an erythroblastotic infant is Rh–, while the father is Rh_1 or, occasionally, Rh_2. It is for this reason that the anti-Rh_1 serum is not as satisfactory as a routine diagnostic reagent as the other two sera. In other words, there are a small number of cases of proved erythroblastosis fetalis in which evidence of isoimmunization (father, +; mother, –) could not be obtained with the anti-Rh_1 serum but only with the other two sera. An example is given in Table III.

TABLE III

	ANTI-Rh′	ANTI-Rh	ANTI-Rh′
Father	+	+	0
Mother	0	0	0
Child	+	+	0

Of the remaining two varieties, either one is a very satisfactory reagent for the detection of the vast majority of instances of isoimmunization, either by pregnancy or by repeated transfusions. Actually, the anti-Rh serum is slightly preferable to the anti-Rh′ serum because it will also detect the 2 per cent of mothers of erythroblastotic infants whose blood is Rh′. The incidence of this sort of mating is 85 per cent × 2 per cent, or 1.7 per cent. However, the anti-Rh serum will fail to detect isoimmunization in which the father's blood is Rh′ and the mother's Rh–. Instances of this sort which occur in 0.26 per cent (2 per cent × 13 per cent) of all matings can readily be diagnosed with the aid of the anti-Rh′ serum or even with the aid of the Rh_1 serum. Two illustrative cases are cited in Table IV.

TABLE IV

	ANTI-Rh′	ANTI-Rh	ANTI-Rh_1
Father	+	+	+
Mother	+	0	+
Child	+	+	+
Father	+	0	+
Mother	0	0	0
Child	+	0	+

In practice it will be convenient to use an anti-Rh serum in order to detect the great majority of the cases and an anti-Rh_1 serum for the exceptional cases indicated in Table IV. Accordingly, the clinically more important anti-Rh′ serum will be spared, and this is a matter of considerable importance, because potent sera suitable as diagnostic reagents are exceedingly rare.

Standardization of Human Anti-Rh Sera.—Most workers agree that the experimental anti-Rh serum produced by rabbits or guinea pigs

injected with the blood of *M. rhesus* monkeys cannot as yet be used as a routine diagnostic serum. This is most unfortunate because potent anti-Rh sera produced by mothers of erythroblastotic infants are very rare.

Once an anti-Rh serum is observed in a particular case, it is necessary to determine its titer and specificity. Any serum having a titer of at least 1:20 may be considered as a suitable diagnostic reagent. Since each one of the three varieties of anti-Rh sera has its own degree of usefulness for a diagnostic purpose, all sera giving potent reactions should be collected and stored.

The specificity of any anti-Rh serum can readily be determined by comparing the reactions obtained in tests with bloods of varying antigenic composition with these shown in Table II. Unless an Rh′ blood is available, additional tests may be required in order to differentiate anti-Rh from anti-Rh′ sera. Anti-Rh′ sera may react with varying intensities on bloods Rh_1 and Rh_2, because these sera may contain the two agglutinins in unequal titers. From a practical standpoint, it will not prove to be a profitable procedure to determine the specificity of any anti-Rh serum unless it has at least a moderate degree of activity. However, this should be done whenever possible in order to collect data on the variety of anti-Rh agglutinins which can be expected from the contrasting antigenic components of the blood of the mother and the fetus.

Since human anti-Rh sera contain also agglutinins anti-A, anti-B, or both, it is essential to neutralize the activity of the normal isoagglutinins so that bloods of all groups could readily be tested. The simplest procedure is to add one or two volumes of Witebsky's group-specific substances to four volumes of anti-Rh serum.* Obviously, this will not be necessary if the anti-Rh serum is obtained from an individual of Group AB. For some sera, large amounts of the A and B soluble substances may be required for the complete inhibition of the anti-B agglutinin.[13] Occasionally, sera will be observed to exhibit the so-called "zone" effect, which is characterized by weak reactions with serum used undiluted or in low dilutions and stronger reactions with moderate dilutions.[13, 14]

In view of these difficulties of standardization and the rarity of potent anti-Rh sera, it seems advisable for various hospitals to pool their resources to form some central unit to be supervised by a serologist trained specifically for this work. Such an organization should receive the support of the local medical societies and all groups interested in infant and maternal welfare. The functions of this central laboratory should include the preparation of lists of Rh+ and Rh–

*Witebsky recommended the addition of the A and B specific substances for the preparation and transfusion of safe universal donor blood (J. A. M. A. 116: 2654, 1941).

donors, complete blood studies in all cases of unexplained fetal or neonatal morbidity and, of course, tests to select and standardize anti-Rh for diagnostic purposes.

Statistical Proof.—

A. *Incidence of the Rh Factor:* The statistical evidence in support of the role of the Rh factor in erythroblastosis fetalis is indicated in Table V. Fortunately, the most useful diagnostic anti-Rh serum (Mrs. M. F.) was available at the very beginning of these studies.

TABLE V

	PERCENTAGE OF NEGATIVE REACTIONS		
	SERA		
	ANTI-Rh′	ANTI-Rh	ANTI-Rh_1
Random	13	15	27
Mothers of erythroblastotic infants	81	90	77
Number of mothers tested	64	142	39

As indicated in Table V, the anti-Rh_1 serum does not give as good a statistical deviation as the other two sera. Even these results could serve as a basis for the theory on the pathogenesis of erythroblastosis, except that an explanation for the isoimmunization in 23 per cent instead of only 10 per cent of the mothers would have to be provided.

Actually, the results with the anti-Rh′ serum would closely approximate those obtained with the anti-Rh serum since all but two of the eighty-four mothers not tested with this serum could be classified as negative.

The confirmatory findings of other workers are recorded in Table VI.* It is assumed that the serum employed was either anti-Rh or anti-Rh′ in specificity.

TABLE VI

AUTHORS	NUMBER OF MOTHERS OF ERYTHROBLASTOTIC INFANTS	
	Rh+	Rh–
Boorman, Dodd, and Mollinson[16]	2	46
Potter, Davidson, and Crunden[17]	6	54
Brewer[18]	0	5
Wiener[19]	6	37
Race and associates[20]	6	44
Total number	20	186
Per cent	9.7	90.3

Based on the tests with the anti-Rh serum, eighty-nine husbands and seventy-six affected infants in the series of 141 Rh– mothers were all Rh+ in accordance with the theory. In a random population, one should have expected thirteen husbands (89 × 15 per cent) and eleven infants (76 × 15 per cent) to be Rh–.

*The series of twenty cases of Gallagher, Danis, and Jones[15] are not included here because of insufficient evidence of erythroblastosis fetalis. If one excludes five infants with moderate jaundice, there remain four Rh+ mothers and eleven Rh– mothers.

Accordingly, the incidence of the Rh factor in three selected populations—the mother, the father, and their erythroblastotic infant—varies markedly from that of the random population. The statistical deviation is most striking in the mothers, so that in the presence of a suggestive history (fetal or neonatal morbidity) isoimmunization by the Rh factor can be suspected if only the mother's blood is tested, provided that it is Rh– or Rh′. Actually, the statistical chances for confirming the diagnosis of erythroblastosis fetalis are much better if Rh tests are carried out on the mother's blood alone than on the affected infant's blood alone. However, in practice, Rh tests should be carried out not only with the bloods of the three persons involved, but also with the blood of the surviving children, if any. Complete observations on all members of the family are useful not only for the collection of data for subsequent analysis, but also for the prognosis of future pregnancies. These data on the contrasting antigenic structure of the bloods of the three persons involved is important in connection with the variety of anti-Rh agglutinin which the mother may produce.[13, 21]

B. *The Incidence of Anti-Rh Agglutinins in Rh– Mothers:* The final proof for isoimmunization is the demonstration of anti-Rh agglutinins. Obviously, the chances for their detection are greater if the tests are carried out soon after delivery (Table VII).

TABLE VII

INCIDENCE OF ANTI-RH AGGLUTININS IN 141 RH– MOTHERS*

INTERVAL AFTER LAST DELIVERY OF AN AFFECTED INFANT	AGGLUTININS PRESENT	AGGLUTININS NOT FOUND
2 months post partum	33	37
2 months to 1 year post partum	5	15
1 year or longer post partum	2	39
During next pregnancy	2	5
No data	0	3
Total	42	99

*From Levine and associates.[7]

It is significant that anti-Rh agglutinins could not be demonstrated in somewhat more than 50 per cent of the mothers in tests carried out shortly after the delivery.* It is now established that isoimmunization may occur even in the absence of demonstrable antibodies.[8, 22] The assumption may be made that antibody production has occurred, but since the antibodies are fixed to the cells of the reticuloendothelial system, they are not released into the circulation. This seeming discrepancy is of considerable practical importance because even Rh– mothers of erythroblastotic infants with no agglutinins in their serum are subject to serious transfusion reactions if Rh+ blood is administered. At least one case† of this sort resulting in a fatal anuria is

*A higher incidence of anti-Rh agglutinins in mothers of erythroblastotic infants is reported by the British workers.[26, 30]

†Blood studies in this case were made with Dr. L. Burnham.

included in the series presented in Table V. Additional evidence is derived from the high incidence of transfusion reactions in the group of patients immunized by repeated transfusions of Rh– blood.

These findings indicate that for the prevention of transfusion accidents, tests of the red blood cells with anti-Rh diagnostic sera are far more important than tests for the presence of atypical agglutinins. In other words, Rh– patients immunized either by pregnancy or by previous transfusions will tolerate transfusions of Rh– blood only. It is probable that once an Rh– individual is immunized, this person remains immunized for the remainder of his or her lifetime.[13] Accordingly, the proper selection of donors for this group of cases is also applicable if the transfusion is to be carried out many years later, even in the period considerably beyond the child-bearing age.*

In contrast to the high incidence of Rh– mothers with no demonstrable agglutinins, several cases have been observed in which anti-Rh agglutinins diminish in activity very slowly so that they may still be present one or even several years after the delivery of an erythroblastotic infant. This long duration is probably a manifestation of intense isoimmunization and may perhaps influence the outcome of the following pregnancy with an Rh+ fetus. In this connection it is significant that mothers of erythroblastotic infants have a higher than normal incidence of abortions and miscarriages. Indeed, prior to the studies on the Rh factor, Macklin[23] suggested that the same mechanism causing the disease in the fully or almost fully developed fetus or infant may become effective in the early fetus. This view of Macklin's is fully supported by the occasional occurrence of intragroup transfusion accidents in women following an abortion or miscarriage.[7]

Rh+ Mothers of Erythroblastotic Infants.—In this series and in a subsequent series of cases mentioned elsewhere, it was observed that a greater number of doubtful cases of erythroblastosis fetalis occurred in the group of Rh+ mothers.[13] Nevertheless, an explanation for the isoimmunization in this smaller group of cases, the corrected incidence of which may be 7 or 8 per cent instead of 10 per cent, is to be provided. Since it is not likely that an entirely different mechanism is responsible for these cases, one may assume that factors in fetal blood, other than Rh, may also induce isoimmunization of the mother.

Perhaps the most surprising outcome of the studies in isoimmunization by the fetus is the prominent role played by only one factor. On the basis of the experience with the individuality of human, and especially animal blood, one should have expected to find numerous blood factors capable of inducing isoimmunization either by pregnancy or by repeated blood transfusions.

Actually, an atypical agglutinin produced by an Rh+ mother of an erythroblastotic infant was found by Levine and Javert[7, 24] early in

*Similar observations were made by Weiss (oral communication).

the course of these studies, and another case was observed recently.[13] This immune agglutinin reacted distinctly on all Rh– and Rh_2 bloods. The remaining bloods either gave negative or very weak reactions. Accordingly, the agglutinable factor demonstrable by this new agglutinin has some genetic relationship to the Rh factor. For this reason the two letters in Rh were reversed, and the terms Hr and anti-Hr were selected to designate this new blood factor and its corresponding antibody.[25]

More recently, Race and Taylor[26] observed a potent agglutinin apparently of the anti-Hr type produced by an Rh+ mother of an erythroblastotic infant. Because their serum gave far more potent reactions than the anti-Hr serum of Levine and Javert, the British workers were in a position to suggest that these sera may possibly differentiate bloods homozygous and heterozygous for the Rh factor. Further reference to this clinically important subject will be found below (page 667).

In any event, the demonstration of an immune agglutinin of whatever specificity, provided that it agglutinates the blood of the father and the affected infant, satisfies the criteria of isoimmunization by pregnancy. So far as the Hr factor is concerned, its role in any particular case can be suspected if the father is Rh– or, perhaps, Rh_2, and the mother is Rh+.

However, the Hr factor can be held responsible for isoimmunization in only some of these Rh+ mothers. In a certain number of the remaining cases, isoimmunization may perhaps be induced by the factor A or B in fetal blood.[7, 27] Evidence for the capacity of these factors to induce isoimmunization is derived from two sources of observations. In both instances specific increases of the normally present isoagglutinin anti-A or anti-B have been observed either following transfusions of group incompatible blood or after delivery of a normal infant, most frequently the firstborn (Jonsson[28]). At any rate, isoimmunization by the factor A or B in fetal blood as the cause of erythroblastosis fetalis can be suspected if both parents are either Rh– or Rh+, but the dominant factor A or B is present in the father's but not in the mother's blood. The demonstration of a specific increase of agglutinins when present is confirmatory evidence.

In this connection mention may be made of the wide distribution of the A and B factors in tissue cells and body fluids in contrast to the presence of the Rh factor in red blood cells only.[29, 30] The role of the factors A and B in erythroblastosis fetalis and its relationship to secretors or nonsecretors of these substances is still to be investigated.

In a few instances, a specific difference in the bloods of the father and the mother could not be demonstrated by means of agglutinins for the factors Hr, A, or B. There are several other possibilities of resolving these cases such as the atypical hemolysin of Levine and Polayes,[31] antibodies which detect still finer differences in the Rh antigenic complex, and other rare isoantibodies observed in patients fol-

lowing repeated blood transfusions. Unfortunately, these reagents are not readily available.

Because of the lower incidence of the Rh+ mothers of erythroblastotic infants, statistical proof for the role of the factors Hr, A, and B, analogous to that provided for the Rh factor, cannot be supplied at present. In the absence of atypical antibodies or specific increases of the normally present anti-A or anti-B isoagglutinins, it seems advisable to require more rigid clinical and pathologic diagnostic criteria of erythroblastosis fetalis in the entire group of Rh+ mothers.

The Familial Incidence of Erythroblastosis Fetalis.—An analysis of the obstetric histories of mothers of erythroblastotic infants reveals a very high incidence of affected infants in some families and a very low incidence in others. In the former case, it is characteristic that all, except perhaps the first one or two infants, are affected. In the contrasting history, only one out of several children has erythroblastosis fetalis. In terms of the isoimmunization theory, these seemingly discrepant observations are readily explainable, and the essential feature is the genetic constitution of the father's Rh+ blood.[7, 32]

For the sake of clarity, one may assume a very simple mode of heredity of the Rh factor so that there are two genetic sorts of RH+ individuals: RhRh (homozygous) and Rhrh (heterozygous) and only one variety of the Rh– individuals, rhrh. Genetically, there are two sorts of matings in which isoimmunization by the Rh factor may occur. In the one, the father is homozygous, in which case the fetus in every pregnancy must be Rh+. Accordingly, each pregnancy offers an opportunity for the immunization of the Rh– mother. In the other mating in which the father is heterozygous, 50 per cent of the offspring will be Rh+ and 50 per cent will be Rh–. In either mating the first one or, perhaps, two pregnancies with Rh+ fetuses may be required to initiate a sufficient degree of isoimmunization. Once the Rh– mother is immunized, all subsequent pregnancies with Rh+ fetuses terminate in one of the several clinical varieties of erythroblastosis fetalis.* It is evident that Rh– fetuses cannot immunize the Rh– mother.

With the aid of anti-Rh sera alone, it is not possible to differentiate serologically homozygous and heterozygous individuals. Genetic proof that the father is heterozygous can be obtained if one of the surviving children is Rh–. Since 50 per cent Rh– offspring can be expected in such a mating, further pregnancies may be recommended. If, however, the first one or two children are normal and Rh– and the next two pregnancies result in affected infants, the chances are that the father is homozygous. In view of tremendous pregnancy wastage in matings of this sort, further pregnancies should be discouraged and, as an alternative, adoption may be recommended.

*Very early in the course of these studies it was observed that two Rh– mothers with anti-Rh agglutinins had presumable normal babies.[4-6] At least one of the infants was Rh+. Unfortunately, hemological and clinical data are lacking to determine the presence or absence of a very mild form of anemia. A similar case was recently observed by Sachs in Dublin.[33]

Recent observations, however, point to the possibility of differentiating homozygous and heterozygous individuals with the aid of anti-Hr sera. In view of the complex structure of the Rh antigen, one may assume at least four genes, Rh_1, Rh_2, Rh′, and rh.* The first three genes determine the presence of the corresponding blood properties as indicated in Table II. Since every blood failing to react with anti-Rh_1 serum is strong with the anti-Hr type of serum, it must contain the Hr factor. In the genotypes indicated in Table VIII, bloods containing the Rh′ antigen are not included since this comprises only 2 per cent of all bloods. The reactions to be expected with potent anti-Hr sera are also given.

TABLE VIII

PHENOTYPE	GENOTYPE	REACTIONS WITH		
		ANTI-Rh	ANTI-Rh_1	ANTI-Hr
Rh_1	Rh_1 Rh_1	+	+	0
	Rh_1 Rh_2	+	+	±
	Rh_1 rh	+	+	±
Rh_2	Rh_2 Rh_2	+	0	+
	Rh_2 rh	+	0	+
Rh–	rh rh	0	0	+

It must be borne in mind that potent anti-Hr sera are exceedingly rare and, with the only ones available, it is not possible to detect the weaker reactions. Judging from the recent report of Race and Taylor, the only type of blood failing to react with their potent anti-Hr type of serum is homozygous for the Rh_1 factor. This type of blood is more frequent than the other forms which, from the point of view of isoimmunization, may also be considered as homozygous; i.e., Rh_1Rh_2 and Rh_2Rh_2. This clinically important aspect requires the accumulation of more data based on genetic studies with potent anti-Hr sera in order to determine whether or not gene Hr can replace gene rh in the genotypes given above.

Erythroblastosis fetalis serves as the first known example of selective fetal or neonatal morbidity due to a genetic and constitutional difference in a normal blood property. It is evident that in the series of Rh– mothers the Rh– infants must be normal and all affected infants must be heterozygous Rh+.† In this connection, the Rh findings in nonidentical twins, one of whom is normal and the other erythroblastotic, are of special significance. In each of four sets of twins, the normal member was Rh–, while the affected one was Rh+.

Reference to this selective disease in twins was made previously.[34] In a second case studied recently, evidence of isoimmunization could be obtained only with the aid of the anti-Rh′ serum, because the affected twin had the rare property Rh′.‡ A third case was studied by

*This genetic theory was first proposed by Wiener and Landsteiner.[11]

†An Rh– (rhrh) mother cannot give birth to a homozygous Rh+ (RhRh) infant.

‡This case was studied with Mr. R. K. Waller.

Guest,* and a fourth was published recently by Kariher.[35] The incidence of nonidentical twins is 1:90 deliveries, while that of erythroblastosis fetalis can now be given as about 1:200 deliveries instead of 1:438. Accordingly, the combined events can be expected to occur about once in 1:18,000 deliveries.

It is of interest that in somewhat more than one-seventh of all random matings the father is Rh+ and the mother is Rh–. This is based on the use of the anti-Rh serum; i.e., 85 per cent × 15 per cent = 13 per cent. Accordingly, one would expect a much higher incidence of erythroblastosis fetalis than the value of 1:200 full-term deliveries based on Rh tests as well as on clinical and pathologic diagnosis. This gap is bridged by several factors of safety, the most significant of which has been the tendency toward small families. Obviously, with a higher degree of parity, the isoimmunization becomes increasingly more marked. But in more than one-half of the susceptible matings in which the father is heterozygous, only 50 per cent of the offspring could immunize the mother. There are probably numerous families with a homozygous father, but all children may be normal if the mother is genetically incapable of producing antibodies. It is probable that for every family in which even the first Rh+ child is affected, there is at least an equal number of families in which the first three or more Rh+ children are normal.

Racial Differences in the Incidence of Erythroblastosis Fetalis.—Further support for the isoimmunization theory has recently been derived from the varying incidence of the Rh factor in several different races. These results indicate that, remarkably enough, the incidence of the disease in infants of any race is directly proportional to the incidence of Rh– individuals, male or female, in the random population[12] (Table IX).

TABLE IX

TESTS WITH ANTI-RH SERUM

RACE	NUMBER TESTED	+ (%)	– (%)	INCIDENCE OF ERYTHROBLASTOSIS FETALIS (%)
White[a]	334	85.0	15.0	2.1
Negro[b]	264	95.5	4.5	0.7
Negro[c]	113	92.0	8.0	
American Indians[d]	120	92.2	0.8	?
Chinese[e]	150	99.3	0.7	Very rare

[a]Levine, Katzin, Burnham, and Vogel.[7]
[b]Levine.[13]
[c]Landsteiner and Wiener.[9]
[d]Landsteiner, Wiener, and Matson.[36]
[e]Levine and Wong.[37]

The most striking variations hitherto observed are found in white and Chinese races. Thus, Rh– reactions are twenty-one times more

*Oral communication.

frequent in the former race, so that the incidence of the disease in Chinese infants could be assumed to be exceedingly rare. A survey of the literature and the personal experience of obstetricians in China fully support this view. Judging from the racial differences of Rh-reactions in the white and Negro individuals, one should expect three times more erythroblastosis fetalis in the former, and this is supported by Potter's findings based on autopsies of newborn and stillborn infants.[38] Accordingly, erythroblastosis fetalis should be as rare in American Indians as it is in Chinese.

The observations reported above can be demonstrated with the use of either one of the two more important diagnostic sera, anti-Rh and anti-Rh′. Furthermore, these racial studies give support to the view that the anti-Rh_1 serum is not the reagent of choice for the routine diagnosis of erythroblastosis fetalis or the prevention of intragroup transfusion reactions. This is indicated in the results given in Table X which fail to show any correlation with the incidence of erythroblastosis fetalis.

TABLE X

TESTS WITH ANTI-Rh_1 SERUM*†

RACE	NUMBER TESTED	PERCENTAGES	
		+	−
White[a]	334	73	27
Negro[b]	118	46	54
American Indians[d]	69	58	42
Chinese[e]	150	93	7

*Follow key to authors given in Table IX.
†From Levine.[12]

Obviously systematic investigations of other races are desirable both from a clinical and anthropologic point of view.

Mechanism of Transplacental Isoimmunization.—In contrast to the blood factors A and B, the Rh factor is limited to red blood cells. There is reason to believe that the Rh factor is already present in the very young fetus.[39] At present there is no direct proof that the fetal red blood cell—a large formed element—finds its way into the maternal circulation. Obviously the placental barrier is believed not to permit the passage of formed elements. Nevertheless, the data on the pathogenesis of erythroblastosis fetalis permit of no other conclusion.

The only assumption that can be made is that minute quantities of fetal blood do penetrate the barrier. With this in view, attempts were made to demonstrate that minute quantities of blood suffice for immunization. Thus distinct increases in agglutinins were observed in each of five rabbits after fourteen daily injections of 2 c.c. of 1:5000 suspension of human blood, or a total volume of 0.0028 in terms of sediment. The corresponding value for a woman weighing 120 pounds is only 0.0672 red blood cell sediment.[13]

In this connection it is significant that the course of the pregnancy and the delivery of the mother of the erythroblastotic infant is entirely uneventful in the vast majority of cases. Accordingly, one need not assume the presence of gross, readily detectable, lesions in the placental barrier, as suggested by Javert.[40] In view of the vast surface area of the fetal villi exposed to the maternal blood stream, it is not improbable that minute amounts of fetal blood slowly enter the maternal circulation without disturbing the course of the pregnancy. According to Dodds,[41] the total area of the fetal villi of a human term placenta exposed to maternal sinuses is 70 sq. ft., and the total length of these villi, if laid end to end, would measure 11.4 miles.

As a corollary of the proposed hypothesis, one must assume that the passage of fetal red blood cells into the maternal circulation is not limited to Rh– mothers but rather that this phenomenon is present in every normal pregnancy. More specifically, isoimmunization by the Rh factor may occur in only those matings in which the father is Rh+ and the mother is Rh–. Obviously, the fetus must be Rh+ and the mother must have the genetic capacity to produce antibodies. Broadly speaking, the same mechanism brought about by the other blood factors may result in early or late fetal or neonatal morbidity other than erythroblastosis fetalis. In this connection, mention may be made of the large group of miscarriages and stillbirths of unknown etiology, and preliminary findings with the blood factors A and B have already been reported.[27, 34]

Some Practical Applications.—

1. A method is now available to prevent intragroup transfusion reactions in Rh– patients immunized either by the Rh+ fetus or by repeated transfusions of Rh+ blood. From the pediatric point of view it may be noted that 15 per cent of children requiring repeated blood transfusions are Rh– and that some of them will be immunized after a variable number of transfusions. For all subsequent transfusions, only Rh– blood must be used. It is now possible for each hospital or donor bureau to have a list of Rh– donors available.

2. The value of Rh tests in establishing the diagnosis of erythroblastosis fetalis has already been discussed. The results fully justify the contention of Diamond, Blackfan, and Baty,[42] that anemia of the newborn infant is one of the several manifestations of erythroblastosis fetalis.

3. A prognosis for the outcome of future pregnancies of mothers of erythroblastotic infants may be made on the basis of Rh tests. The value of this test hitherto was limited only to those matings in which at least one of the surviving children is Rh–. This is proof that the father is heterozygous, so that there is a 50 per cent chance for future Rh– offspring in such matings. As already indicated, it is probable that

more direct differentiation of individuals homozygous and heterozygous for the Rh factor may be made with the use of the anti-Hr serum.

4. Of more immediate importance to the pediatrician is the recommendation that the affected infant be transfused with Rh– blood. Obviously this subject merits a fuller discussion.

The Treatment of Erythroblastosis Fetalis With Transfusions of Rh– Blood.—Since the hemolytic process is still active in the early neonatal period, the Rh+ blood of the infant, or any Rh+ blood which may be transfused, is still susceptible to the action of the presumably stored anti-Rh agglutinins.* Accordingly, it was suggested by Katzin, Vogel, and Levine[43] that the affected infant be transfused with Rh– blood. In a small number of cases, it was observed that the transfused Rh– blood survives for long periods so that the normal increment of red blood cells and hemoglobin expected from a compatible transfusion is maintained. In one case studied by Brown and Levine[44] in September, 1941, the Rh+ blood of the affected infant was almost entirely replaced by the transfused Rh– blood. The destruction of the infant's own Rh+ blood was so complete that only very few small and scattered clumps could be observed in tests with potent anti-Rh sera. The findings in this case which may be considered typical are reproduced in Table XI.

TABLE XI*

AGE	TRANSFUSION (C.C.)	R.B.C.	HB.	ICTERIC INDEX	TEST WITH ANTI-Rh SERA
8 days	90† (A.M.)	2.30	9.5		
8 days	80† (P.M.)	2.19	7.0	48	++
9 days	105†	1.80	7.5		
10 days	150	2.91	7.0	60	
11 days		3.95	12.0	48	– except for occasional clumps
12 days		6.58	15.5	30	
15 days		3.85	16.0	24	– except for occasional clumps
19 days		4.01	12.0	11	
28 days		4.20	14.0		
		Six-Month Interval			
7 months		5.55	14.8		++

*From Brown and Levine.[44]

†Indicates mother's blood used for transfusion. The fourth transfusion (150 c.c.) on the tenth day was from a male Rh– donor.

Early in the course of these studies, it became evident that the mother's Rh– blood is not to be used for transfusing the infant, because of the administration of the accompanying anti-Rh agglutinins. In one of the earliest cases studied with Vogel, the transfusion of the mother's blood (M. F. in Table I) was followed by increase of the jaundice, fever, and hemoglobinuria. The result of transfusion with the mother's blood is further indicated in the data presented in Table XI since the clinical improvement of the infant and the cessation of the hemolytic process was not observed until a random Rh– donor was used instead of the mother's blood, which contained anti-Rh agglutinins.

*See page 673.

Actually, the mother's blood may be used, if compatible, provided that the plasma be removed and replaced by saline or inactive plasma of the same blood group.[32] It is probably not necessary to wash the mother's Rh– blood for the complete removal of her plasma.

Similar cases with dramatic recovery following the use of Rh– blood have been observed by Boorman and associates[16] and more recently by Wiener and Wexler.[45]

DISCUSSION

The earlier theories on the pathogenesis of erythroblastosis fetalis were reviewed in an excellent paper by Darrow.[46] In a sense, this author anticipates an antigen-antibody reaction which "seems to explain best all aspects of these related disorders." In her opinion, the antigenic material may have been derived from a specific difference in the hemoglobin of the fetus and the mother. The possibility of isoimmunization was also mentioned previously by Ottenberg,[47] who was influenced by the early papers of Dienst[48] on placental transfer. At any rate, the studies on isoimmunization by the Rh factor establish that in erythroblastosis fetalis there is no congenital defect in the red cells.

The remarkably varying clinical manifestations of erythroblastosis fetalis are entirely compatible with the isoimmunization theory. One may assume that fetal hydrops is the end result of intense isoimmunization over a prolonged period, while anemia of the newborn infant is the condition to be expected from a shorter duration of the same process. By the same token the two extreme forms should be rare in contrast to the more frequent intermediate variety, icterus gravis. Studies are still required to determine the exact time and the conditions during pregnancy when isoimmunization is initiated.

Now that the source of the intrauterine hemolysis is established, there is no conflict whatever between the striking variations in clinical manifestations and the one uniform characteristic pathologic feature of blood destruction and extramedullary hemopoesis.

Nevertheless, one manifestation of erythroblastosis fetalis cannot be reconciled readily with the isoimmunization theory. One should expect erythroblastosis fetalis to be a disease exclusively of the fetus, with spontaneous cure at birth. Since the source of the intrauterine hemolysis of fetal blood is derived from the action of maternal anti-Rh agglutinins, all further blood destruction should cease immediately after delivery. This does not correspond with the clinical characteristics of the disease, so that it becomes necessary to seek an explanation for the rapidly increasing jaundice and anemia in the neonatal period. That the same antigen-antibody reaction is responsible for the symptoms in the neonatal period is indicated by the dramatic improvement following transfusions of Rh– blood. Accordingly, the infant's Rh+ blood is still undergoing specific destruction, and it must be assumed that maternal anti-Rh agglutinins are still active.

It has been suggested that the source of the delayed hemolysis may be colostrum, but many of these infants are not breast fed.* An alternative explanation is the storage of anti-Rh agglutinins in the fetal tissues and their liberation soon or shortly after delivery. However, this would involve the simultaneous presence of maternal anti-Rh agglutinins and its corresponding antigen in the blood stream of the affected infant. Actually, the survival of maternal anti-Rh agglutinins in the infant has been demonstrated but rarely. Obviously there is an excess of fetal Rh+ cells which should bind and neutralize the maternal anti-Rh agglutinins.† In the absence of further data, the mechanism of the delayed hemolysis remains unexplained.

Finally it should be mentioned that Smith[50] and Kariher and Spindler[51] recently suggested that the term erythroblastosis fetalis be replaced by "hemolytic disease of the newborn," or "hemolytic disease of the fetus and the newborn." In view of the findings presented, there seems to be some justification for a change in the terminology.

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*That anti-Rh agglutinins pass from the blood into the colostrum has been demonstrated by Witebsky.[49]

†The simultaneous presence of antigen and antibody has been observed in at least two Rh⁻ patients who had suffered from violent hemolytic reactions following the transfusions of Rh+ blood. One of these was studied with Dr. Katzin.

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PHYSIOLOGY OF THE HEMATOPOIETIC SYSTEM IN INFANTS AND YOUNG CHILDREN, INCLUDING THE BLOOD PICTURE AT BIRTH AND IN YOUNG INFANTS

PEARL LEE, M.D.
DETROIT, MICH.

THE physiology of the hematopoietic system in infants and young children is very imperfectly understood. Consequently, explanations for the blood pictures peculiar to this age group must be largely theoretical. The type of blood found in the newborn infant is never seen normally at any other time of life. Soon after birth, a series of remarkable changes is initiated. These changes are especially striking during the first six months. By the end of the second year, the picture is approximately that of the adult.

In Table I are presented average figures for the blood of normal infants from birth to 2 years of age. These figures have been selected from various sources and reflect my personal opinions.

It may be seen from the table that the newborn infant has a very high hemoglobin and a moderately high red blood cell count with reticulocytes and a few normoblasts. Cells more immature than the normoblast are pathologic in the full-term infant but may occur in the premature. The mean corpuscular diameter is large, being 8.6, while the adult average is from 7.2 to 7.4. This large size is reflected in the high hematocrit.

The white cell-forming tissues are also very active, producing a total white count that averages from 10,000 to 20,000 at birth. However, there are many lower and higher figures. Neutrophiles make up 60 to 70 per cent of the differential. Myelocytes are rare in the full-term infant but are seen frequently in the premature.

A few investigators have found the platelet count to be slightly high at birth but usually it does not show any marked variations.

The premature infant has the same general blood picture as the full-term one, but every element is more exaggerated. The hemoglobin and red and white blood cell counts are all higher. Immature red blood cells are more numerous and sometimes earlier forms than the normoblast appear.

Within a few days after birth, a rapid decrease in hemoglobin and red blood cell count begins. When the infant is 2 weeks of age, the hemoglobin has fallen 3 or 4 Gm. and the red blood cell count, about one million. Normoblasts disappear within two or three days or one week at the most. Reticulocytes also begin to decrease. This rapid fall continues and reaches its lowest point usually by the eighth or tenth week. At the same time, the cell diameter also decreases to the adult size.

TABLE I

AGE	HB. (GM. PER 100 C.C.)	R.B.C. (MILLIONS PER C.MM.)	HEMATOCRIT (VOL. %)	RETICULOCYTES (% R.B.C.)	NORMOBLASTS (PER C.MM.)	MEAN CORPUS DIAM. (μ)	W.B.C. (PER C.MM.)	POLYMORPHONUCLEARS (PER CENT)	LYMPHOCYTES (PER CENT)	COLOR INDEX
24 hr.	18 to 22	5.0 to 6.0	54 ± 10	3.0	400 to 500	8.6	10 to 20,000	60 to 70	20 to 30	1+
2 wk.	15 to 20	4.5 to 5.5	49		None			30	60	1+
4 wk.	14 to 16	4.0 to 5.0	42		None					
2 mo.	10 to 14	3.5 to 4.5		0.5	None					
3 mo.	10 to 14	3.5 to 4.5	36	2.0	None	7.3				
6 mo.	11 to 14	4.0 to 5.0	35	0.5	None		10 to 12,000	30	60	1-
1 yr.	11 to 14	4.0 to 5.0	35	0.5	None			40	55	
2 yr.	12 to 14	4.0 to 5.0	35	0.5	None			45	50	
Adult (♀)	13 to 15	4.5 to 5.0	42 to 45	0.5		7.2 to 7.4				

The white count gradually drops to an average of 10,000 to 12,000 at six months. During the first two weeks, there is a rapid shift in the differential from a high percentage of neutrophiles to a preponderance of lymphocytes. At two years, the lymphocytes are still slightly in the majority.

The high hemoglobin and red blood cell count present at birth are developed during the last few weeks of fetal life. The primitive red cells appearing early in the embryo are large and enucleated. About the fourth month, the formation of true red blood cells begins. The concentration of hemoglobin and red cells is still low at this time.

The development of the white cells occurs simultaneously with the second type of red cells in the bone marrow, liver, spleen, and lymphatic tissues.

As the fetus develops, there is a slow rise in hemoglobin and red cells with a reduction in red cell diameter and in the number of immature forms. These changes continue up to birth and for a few hours afterward.

The blood-forming tissue is very extensive at birth. Not only does red marrow fill the cavities of all the bones but islands of erythrogenic tissue are present in the liver, spleen, and most of the lymphatic tissues. The production of erythrocytes and myeloid leucocytes in the extramedullary foci ceases immediately. However, the lymphatic organs continue to develop and are probably responsible for the preponderance of lymphocytes in infancy.

The reason for this very extensive, blood-forming tissue and the accompanying blood picture has been the subject of much controversy. The most commonly accepted theory is that the low oxygen tension in intrauterine life produces the typical blood of the newborn infant in the same manner that polycythemia is produced in adults at high altitudes. However, normoblasts and increased white blood cell counts are not usually found in individuals living in rarefied atmospheres. Probably other factors are also involved in the infant.

The marked changes in the blood picture beginning within the first few days of life are no doubt due to the very radical changes in the new infant's environment. He is suddenly removed from a parasitic existence to that of an independent individual who must establish new equilibria for all its body processes. For this reason the young infant is a very unstable organism. The blood-forming tissues share in this general instability. Trivial causes may produce wide fluctuations in the blood picture. The sudden removal from a low to a relatively high oxygen tension may be the main mechanism initiating the early and rapid decrease in hemoglobin and red blood cell count. This reduction must be accomplished either by a decrease in blood formation or an increase in destruction or a combination of both.

There is evidence to suggest that both occur. Decrease in production is indicated by a disappearance of normoblasts and a reduction in reticulocytes. Increased destruction is manifested by "physiological" jaundice and increased pigmentation of the blood serum. The most widely accepted mechanism for the rapid change in the blood has been this speeding up of the destructive process.

Hemolysis in the newborn infant can easily become severe enough to produce an acute hemolytic anemia. Sometimes it occurs as the result of infection or by isoimmunization as in erythroblastosis fetalis.

The fall in hemoglobin and red blood cells reaches its lowest point when the infant is around 6 or 8 weeks of age. Often the reduction is excessive, producing what might be called a moderate anemia. This is probably due to a lag in the recovery process from what might be called a mild hypoplastic state. Several investigators have proved that the administration of iron will not affect the blood picture before six or eight weeks. Apparently the factors influencing the hemoglobin and red blood cell count in the early weeks are physiologic or intrinsic. After that time, extrinsic factors such as diet, administration of iron, and infections become increasingly important.

At three months the reticulocyte count rises slightly preceding an increase in the red blood cells.

The hematocrit falls to 35 volumes per cent, the lowest normal limits, at six months. It remains near this level throughout childhood.

Between six months and one year there is very little change in the blood picture. At two years it approaches the adult standard.

SUMMARY

The newborn infant begins life with a type of blood picture peculiar to its age group. It is characterized by an increased number of most of the blood elements with a few immature cells. Rapid changes, caused mostly by physiologic factors, take place during the first few weeks reducing the hemoglobin and red blood cell count markedly. After three months a slow recovery begins.

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DISEASES OF BLOOD IN INFANTS AND YOUNG CHILDREN, INCLUDING THE HEMORRHAGIC STATES

H. G. Poncher, M.D.
Chicago, Ill.

THE broader clinical aspects of diseases involving the blood and blood-forming organs constitute an important part of the daily practice of every pediatrician. This fact is not generally appreciated, and all too commonly one is likely to think of this phase of medicine as consisting of rare blood dyscrasias. This traditional point of view stems partly from early training in medical school where a colored plate of blood cells or a diagram indicating their much debated ancestry is held in greater esteem than a clear concept of the nature and functional relationship of the hematopoietic organs. Restricted thinking along the lines of morphologic hematology has resulted in our tendency to categorize and classify rather than to evaluate and interpret. Apart from the well-recognized diseases of the blood-forming organs, the daily work of the practicing physician in clinical hematology is concerned with well-defined reactions to a large variety of stimuli which act on the circulating blood cells or the blood-forming organs.

Accordingly, when diseases of the blood and blood-forming organs in infancy and childhood are considered, we must not think of the subject merely as a chronologic division in the subject of hematology for the purpose of didactic consideration. While it is true that the general nature of etiologic agents which affect the blood and blood-forming tissues of adults may be the same, the reaction of these tissues may be quite different. This difference is a product of the anatomic aspects and the functional response of the blood-forming organs that are found at the pediatric age period. Some of these may be enumerated and briefly characterized as follows:

1. *Distribution of the Blood-Forming Tissues*

Many tissues which function as hematopoietic centers during fetal life respond readily to functional demand, particularly during infancy. Hence extramedullary sites of blood formations are not infrequently encountered under stress. This accounts for the increased incidence of enlargement of the liver and spleen and rarefactions in the inelastic skeletal framework which has relatively little potential reserve to accommodate a rapidly expanding bone marrow without showing signs of pressure resorption. Such findings are observed in many of the erythroblastic and leucoblastic disorders (Cooley's anemia, sickle cell anemia, congenital hemolytic anemia, and leucosis).

2. *Rapidly Expanding Blood Volume*

Rapid growth with concomitant increase in blood volume renders the infant and child much more susceptible to iron deficiency states than the adult. Heath,[1] in a recent critical review of iron deficiency anemias, expressed doubt whether iron deficiency anemia ever develops from defective intake of iron alone, except where iron is lost by hemorrhage or becomes insufficient through increase in blood volume (growth).

3. *Response of Blood-Forming Tissues*

The hematopoietic tissues show the same instability which is characteristic of organs and tissues during infancy and childhood. Rapidly growing tissue generally is characterized by quick response and early exhaustion. Immature red and white cells appear in the peripheral blood under slight stimulation which would be found in the peripheral blood of the adult only in severe blood dyscrasias. Similarly, on sternal aspiration one is frequently surprised to find a hyperplastic marrow indicating a maturation arrest in infants and children with peripheral leucopenias and anemias, whereas in adults such peripheral blood findings are more often associated with a hypoplastic marrow.

4. *Nature of the Response of the Child to Certain Stimuli*

The question often arises as to whether the response of infants and children to various conditions which produce blood disorders varies in degree or in its nature. Here again the inherent anatomic and physiologic differences dependent upon growth and development play a significant role. The infant or child is particularly predisposed to the noxious effects of infection by virtue of his lack of acquired immunity to many infectious agents and by the imperfect development of natural tissue barriers which keep infections localized. Similarly, the marked vascularity of immature tissue, lack of complete development of the vessel wall, and the increased demand for all tissues generally for vitamin C because of growth make the infant or child peculiarly vulnerable to hemorrhage.

Further examples of important anatomic and physiologic differences and their practical implications could be cited in support of this thesis, but they are readily apparent upon reflection to the average physician who has worked with infants and children. In the ensuing discussion diseases of the blood-forming organs will be considered from the standpoint of orientation only. Only the hemorrhagic states in infancy and childhood will be given detailed consideration.

Anemia in infancy and childhood has occupied the major interest of the clinician and the investigator, and most of our progress has been the result of a more rational understanding of the pathogenesis of this symptom. Since the blood reflects the state of those tissues which contribute to its cellular and chemical composition, it is essential that the physician have a practical understanding of interrelationships of

several physiologic processes which are concerned with the maintenance of normal peripheral blood findings. They may be listed as follows:

1. Synthesis of hemoglobin
2. Regenerative ability of the blood-forming organs and maturation of their products
3. Blood destruction
4. Hemostasis or maintenance of an intact vascular system

Anemia in infancy and childhood as well as in any other period of life may result from a disturbance of any one or a combination of such processes. The factors which operate to bring this about may be (1) inherent in the individual (hereditary, constitutional, or intrinsic) or (2) they may be imposed upon the individual because of infection, nutritional deficiency, intoxication, or hemorrhage.

For many years the exact mechanism of groups of infants presenting jaundice, anemia, and edema in the neonatal period was poorly understood. Diamond, Blackfan, and Baty[2] were instrumental in grouping them for a more rational clinical consideration, and a significant advance was made in understanding their pathogenesis with the introduction of the Rh factor by Levine and his associates.[3] In spite of these excellent contributions there are newborn infants with anemia and jaundice that cannot be assigned to this pathogenesis, the causative mechanism of which must be assigned to other factors that are poorly understood at present. Included is that obscure group of cases labeled aregenerative anemias for want of further information concerning their nature. The course is chronic in spite of therapy with repeated blood transfusions, and in most instances recovery is slow.

The clinical importance of the Rh factor is not confined to the newborn period,[4] and with the more frequent use of blood transfusion as a therapeutic agent, the importance of hemolysins and other hemolytic agents is receiving renewed emphasis and study. The work of Dameshek[5] and his associates has shed considerable light on the mechanism of hemolytic syndromes. It is important for the pediatrician to remember that hemolytic episodes in infants and children not infrequently are heralded by such symptoms as abdominal pain, vomiting, and diarrhea, and the true nature of the disease may escape recognition until signs of anemia and obvious signs of blood destruction are evidenced. The presence of anemia and reticulocytosis even in the absence of jaundice should suggest the possibility of a hemolytic process.

Cooley's erythroblastic anemia has forsaken its swaddling clothes to appear in adults in the cryptic role of target cell anemia. For years it was regarded as an entity confined to the pediatric age period, but through the efforts of Dameshek[6] and Wintrobe[7] and their coworkers particularly it has avoided an anachronistic fate. More recent observations point to the existence of the disease in latent and mild clinical forms, and clinicians should be on the alert to recognize these

cases as well as the classical types. Also formerly regarded as being limited to the Mediterranean races, it has shown a tendency of "going global," as Cooley has pointed out.

The term von Jaksch's anemia still persists in pediatric literature. The number of cases that can be ascribed to this eponymic grouping, however, is steadily decreasing with the more careful study of the underlying cause of anemia and the more direct assignment to a specific pathogenesis.

Banti's syndrome is still a controversial field. The demonstration of a specific cause of thrombophlebitis in the vascular channels of the splenic or portal circuit has given a clear pathogenesis in a small group. Ravenna,[8] reviewing the mechanism of the Banti's syndrome, ascribes the picture to a primary lesion in the small splenic arteries, and these vessels, when so affected, lose their regulatory power and allow an active congestion of the spleen, finally resulting in a fibrocongestive splenomegaly. The cause of the anemia and leucopenia has been variously interpreted. In our study[9] of a group of such cases in children without cirrhosis, the sternal marrow has shown a "maturation arrest" of the granulopoietic tissue in the bone marrow, and the findings appear to suggest a chronic toxic process which appears to suppress the normal delivery of granulocytes from the marrow to the peripheral blood. In advanced cases, when the syndrome has progressed to a stage of cirrhosis of the liver, the sternal marrow shows a shift in erythrogenic tissue toward immaturity similar to that found in patients with atrophic cirrhosis. In contrast to the latter group of cases with atrophic cirrhosis, the anemia in Banti's syndrome is normocytic rather than macrocytic. The beneficial effect of splenectomy is more striking in children than in adults, probably because the patients are subjected to surgery earlier. From the results of our study we may state the following:

1. In the earliest stage of the Banti syndrome the sternal marrow shows a myeloid hyperplasia, with moderate anemia and leucopenia in the peripheral blood. Splenectomy at this stage is most successful and will restore the findings to normal.

2. In the more advanced stages the sternal marrow shows a myeloid and megakaryocytic "maturation arrest" and peripheral blood findings of leucopenia, with neutropenia and thrombocytopenia of a moderate degree. In infants and children splenectomy is still of value at this stage.

3. In the later stages of the disease, where cirrhosis may be surmised, erythroid immaturity is seen with the myeloid "maturation arrest" pattern in the sternal marrow. In adults the results of splenectomy are poor in this stage, but in children the operation may still be of some benefit.

The mechanism of iron deficiency anemias in infancy has also been subjected to more critical evaluation. The factor of deprivation of placental blood at birth has been ably documented by the work of DeMarsh, Alt, and Windle.[10] Their results clearly indicate that immediate clamping of the cord is comparable to submitting the infant to a rather severe hemorrhage. The loss of this important amount of iron reserve is a significant factor in the mechanism of iron deficiency anemias of infancy. Similarly we have broadened our conception of nutritional anemias to think beyond the factor of deficient intake. Most physicians have observed the futility of iron administration in infants with nutritional anemia with active infection and now appreciate that iron deficiency may result from defective synthesis as well as deficient supply.

Anemias designated as hypoplastic on the basis of peripheral blood study have been shown, on study of sternal marrow, to be due to a maturation arrest at the normoblastic level, and many children with such anemias have responded to splenectomy. The specific mechanism of this group of cases is, however, still obscure.

Disorders involving the leucopoietic tissues are not as circumscribed as we formerly believed. More frequent use of sternal marrow aspiration has also shown that granulocytopenia may be associated with a hypoplastic, hyperplastic (with maturation arrest), or a dysplastic marrow. Prognosis is more favorable in those patients in whom the leucopenia and granulocytopenia are on the basis of a maturation arrest if the case is recognized early enough and the causative factor removed to avoid secondary complications due to prolonged depression of the functional elements of defense. This is well illustrated in patients who develop leucopenia and granulocytopenia from sulfonamide drugs or infection. One of the most frequent sources of error in the early diagnosis of leucosis in children is to mistake the clinical picture of anemia, fever, purpura, with or without joint or leg pains, and leucopenia for sepsis or agranulocytosis. This is particularly true where splenomegaly and adenopathy are minimal findings. Acute leucosis in infants and children may be leucopenic throughout the entire course of the disease, and some of the mononuclear cells often designated as lymphocytes are immature cells of mistaken identity. It is interesting to note that this observation is not limited to infants and children. Watkins[11] has previously reported that 45 per cent of the cases of acute leucosis seen at the Mayo Clinic over a four-year period had total white counts of less than 10,000 per cubic millimeter. Study of the sternal marrow in the questionable case of leucosis is a more conclusive aid in diagnosis for the practitioner than is any other phase of the hematologic work-up.

The discovery of vitamin K and its successful application in the prophylaxis of the hypoprothrombinemic states in the newborn period

has revived the interest of the practicing physician in the clinical aspects of blood coagulation. While the intimate phases of the coagulation mechanism are still being debated by investigators in the field, sufficient workable facts have been salvaged for clinical medicine to serve a useful purpose at the bedside. For purposes of orientation one may assume that essentially three fundamental factors may be directly or indirectly concerned with maintenance of a normal hemostatic equilibrium. Bleeding from free surfaces or into the tissues may result from a gross deficiency of any single factor or lesser deficiencies in a combination of factors. The factors which are of clinical importance are as follows:

1. The integrity of the capillaries
2. The composition of the plasma
3. The quantitative and functional state of the platelets

Since the normal function of the blood is to remain fluid within the blood vessel and clotting is only a potential property, the primary factor in any hemorrhage is alteration of the integrity of the vascular wall. Such a defect may result from a change in permeability by trauma, chemical metabolic or bacterial toxins, allergy, vitamin deficiency, endocrine disturbances, or vasomotor disorders. In some cases no extraneous cause can be determined, and the vascular alteration is inherent in the make-up of the individual. The extent of the bleeding is, however, conditioned not only by the magnitude of the vascular defect, but also by the functional status of the clotting components of the plasma and platelets.

The commonly accepted views on blood coagulation and the role of platelets are too well known to require repetition. The following conceptual scheme embracing this information, modified slightly from the one proposed by Quick,[12] has practical value in indicating the etiology and the rationale of therapy:

I. Thromboplastin Deficiency
   A. Lack of thromboplastic substance in the plasma or abnormal resistance of platelets releasing thromboplastin
      1. Hemophilia
      2. Pseudohemophilia (von Willebrand's syndrome) or constitutional thrombopathy
      3. Hereditary hemorrhagic thrombasthenia (Glanzmann[13])

II. Prothrombin Deficiency
   A. Defective supply of vitamin K (transient defect in utilization also possible)
      1. Hemorrhagic disease of the newborn
   B. Faulty absorption of vitamin K
      1. Obstructive jaundice
      2. Severe intestinal disorders

C. Defective utilization or synthesis of vitamin K by the liver
   1. Severe hepatitis or liver damage due to infection, syphilis, cirrhosis, or neoplasm

III. Fibrinogen Deficiency
   A. Congenital or hereditary fibrinopenia (Morawitz[14] and Frank[15])
   B. Extensive liver disease due to chronic infections, neoplasm, cirrhosis, or chemical poisoning (chloroform, phosphorus, etc.)

IV. Increase in Antithrombin (Heparin)
   1. Anaphylactic shock
   2. Clinical heparinization

The theoretical category of calcium deficiency has been purposely omitted from the original tabulation as given by Quick. It would seem unlikely that variations in the concentration of serum calcium would materially affect the clotting time under clinical conditions. Ferguson[16] has shown that the minimum calcium ion concentration for clotting is below the lowest calcium level compatible with life in experimental conditions.

Apart from the differentiation of hemophilia and thrombocytopenic purpura, systematic study of the hemostatic equilibrium is not commonly undertaken in case study as often as it is warranted. It is true that bleeding is often observed in the presence of normal tests of hemostatic function, and abnormal results may be obtained when bleeding is not a prominent clinical feature. Nevertheless, as Lucia and Aggeler[17] have emphasized and ably documented by their data, the frequency and intensity of alterations in the hemostatic tests are greater in those who suffer from abnormal bleeding than in those who do not bleed but suffer from diseases in which hemorrhagic manifestations are likely to occur.

A frequent source of error is often due to the employment of convenient but poorly standardized tests of hemostatic function. The determination of the clotting time using capillary blood is a classic example. While it is true that many of the hemorrhagic states may be phasic in character, and other factors, at present unknown, are not evaluated in tests which are routinely employed, every infant or child with clinically important evidence of hemorrhage is entitled to careful laboratory study.

The following standardized laboratory tests will materially aid an effective diagnostic evaluation of the condition of a patient with hemorrhagic disease:

Bleeding time (Duke or Ivy method)
Clotting time (Howell or Lee and White)
Clot retraction or estimation of the extracorpuscular volume of the clot (Aggeler-Lucia-Hamlin)
Prothrombin time (Quick or micromodifications of the method)

Capillary permeability test (Dalldorf)
Blood ascorbic acid determination
Platelet count (Fonio or counting chamber method)
Fibrinogen (Whipple)

The classical laboratory findings of the common hemorrhagic disorders are well known or readily available in laboratory textbooks. Difficulty often arises in the proper classification of conditions in patients with purpura and thrombocytopenia.

Purpura with platelet reduction is a common manifestation in a wide variety of clinical states in infants and children. Not infrequently where the cause is not readily apparent the diagnosis of idiopathic purpura hemorrhagica (Werlhof's disease) is erroneously made. Wiseman, Doan, and Wilson[18] have crystallized the following useful set of seven essential diagnostic points for Werlhof's disease:

1. There must be spontaneous purpura or free bleeding from the mucous membranes

2. The blood platelets must be substantially decreased in numbers, at least less than 100,000 per cubic millimeter of blood

3. The clotting time and prothrombin time must be within normal limits

4. The anemia and leucocyte count must not be out of proportion to the amount of bleeding

5. No pathologic cells must be present in either the blood or the bone marrow

6. There must be no recent history of ingestion of drugs or the occurrence of any of those diseases known occasionally to produce thrombocytopenia

7. There must be no appreciable enlargement of the spleen or lymph nodes.

Clinicians have often expressed the desirability of having an accurate index for the selection of patients with essential or idiopathic thrombocytopenic purpura who will respond favorably to splenectomy. We have found that the bone marrow megakaryocytic pattern as revealed by sternal aspiration offers such assistance when considered with the other findings.

Limarzi and his associates[19] have found that two types of bone marrow may be observed in essential thrombocytopenic purpura; one is associated with megakaryocytic hyperplasia, and the second type is associated with a megakaryocytic hypoplasia. In the first type, a clinical and hematologic cure consistently results following splenectomy, while in the second type, associated with marked diminution of the megakaryocytes, the failure or stormy postoperative course following splenectomy can definitely be correlated with the inadequate number of platelet-forming cells.

Progress in the therapy of the hemorrhagic states in infancy and childhood is in striking contrast to the large amount of excellent investigative work in this field. Vitamin K has a specific but limited field and is confined to those conditions in which clinical manifestations are based on prothrombin deficiency. In extensive liver damage the therapeutic value of vitamin K is limited and transient.

Transfusion with freshly drawn blood still remains the treatment of choice in hemophilia. It is not generally appreciated, however, that small amounts of blood are efficacious in mild to moderate prolongation of the coagulation time. Where the physician has a patient with hemophilia under his care, it may be practical to conserve his donor supply by giving from 50 to 100 c.c. of blood instead of larger transfusions unless they are indicated because of anemia and reduced blood volume. Instead of waiting for clinical symptoms of hemorrhage to occur, the coagulation time may be studied at routine intervals and small amounts of blood given to keep the coagulation time as close to normal as possible.

One of the most disabling symptoms of hemophilia is the inevitable hemarthrosis, particularly in the knee and elbow joints. This complication is less apt to occur if the coagulation time can be kept as close to normal as possible by small transfusions. We recently subjected a child with known hemophilia to a successful operation for intussusception by giving only 100 c.c. of blood preoperatively and depending upon the prolongation of the clotting time for further indications for transfusions. A total of only 300 c.c. was necessary for the patient's pre- and postoperative course.

Another idea may be tried when donors are difficult to obtain and until a more specific form of therapy is found. Brinkhaus[20] has shown that extremely small amounts of thromboplastin added to hemophiliac blood caused prothrombin to be converted at a normal rate to thrombin. This observation was particularly enlightening, as it has always seemed possible that the individual with hemophilia could theoretically serve as his own donor when one was not immediately available. The blood of an individual with hemophilia apparently has all the potential materials necessary for coagulation except that they are delayed in appearance when blood is shed or measured in vitro (clotting time). Whether this is due to a plasma or platelet factor is still debatable. Since hemophiliac blood clots eventually, the thromboplastic factor must be generated to bring this about. Accordingly, by drawing from 50 to 100 c.c. of blood from a patient with hemophilia and allowing it to stand in citrate for a period of time in excess of his coagulation time, which was previously determined, one should be able to reinject the blood with some therapeutic benefit. I have not had a sufficiently large number of patients to test this hypothesis adequately, but it would appear worthy of trial in an emergency. The addition of from 5 to 10 c.c. of citrated blood from a normal individual to that with-

drawn from the patient might improve the possibility of success, since Bendien and van Creveld[21] and others have shown that the normal plasma contains an activating "globulin" substance which is quantitatively lacking or unavailable in hemophiliac blood.

Another practical point in the management of a patient with hemophilia is the local use of 1:100 epinephrine together with some of the more recent potent thromboplastic substances in the control of free bleeding of the external surfaces of mucous membranes.

The recent work on "vitamin P" (citrin) should be closely followed for its place in the management of the hemorrhagic state. While the use of citrus fruit juices and ascorbic acid has been of value in maintaining the integrity of the vascular wall in the absence of a specific damaging agent, it has not provided the clinician with the complete answer. The existence of a capillary permeability factor in citrus fruits (particularly lemon rind) and other foods (pepper and cabbage) distinct from ascorbic acid was suggested by Szent-Györgyi and his co-workers.[22] These investigators first isolated flavones in crystalline form from lemon, paprika, and green pepper and suggested the term vitamin P. Vitamin P, or citrin, consists of two substances which are now being prepared in pure form by some pharmaceutical houses for clinical trial. They are known as hesperidin and eriodictin, the former being converted into the latter by demethylation in the process of ripening of fruit.

Isolated reports of the use of these substances in pure form appear in literature but as yet evidence of their specific value cannot be stated with certainty. Like vitamin K and other factors which play a specific but limited role in the maintenance of the normal hemostatic equilibrium, the role of vitamin P will be established only by critical evaluation. Its effect appears to be on the vascular factor and not on the intravascular clotting mechanism.

In summarizing this rather brief and incomplete review, one may say that the diagnosis of abnormal bleeding may be grouped into logical categories by means of clinical study and laboratory investigation with standardized tests of hemostatic function. While much remains to be learned of the pathologic physiology of abnormal bleeding, more effective use of information which is already available will result in improved diagnoses and appropriate treatment in the vast majority of pediatric cases. Likewise, the proper assessment of other hematologic symptoms in the light of varying functional and pathologic response of the infant and child will be attended with a greater proficiency in diagnosis and treatment.

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THE DEFICIENCY AND DYSHEMATOPOIETIC ANEMIAS OF INFANCY AND CHILDHOOD

ROY R. KRACKE, M.D., AND WILLIAM R. PLATT, M.D.
EMORY UNIVERSITY, GA.

ALTHOUGH much has been written concerning the blood of infancy, our knowledge today remains incomplete, and many controversial points must still be elucidated. Infancy is a period of life in which anemia is particularly prevalent, and the manifestations of anemias in infants and children differ from those seen in later years. Difficulties are encountered in the diagnosis of anemias because of lack of agreement as to what values for the red blood cells and the amount of hemoglobin constitute normal standards. Hematologic standards for healthy newborn infants have recently been devised by Chuinard, Osgood, and Ellis.[1] They stated that the average erythrocyte count was 4.6 million red cells per cubic millimeter; average hemoglobin concentration, 16.3 Gm. per 100 c.c.; average packed red cell volume, 43.4 c.c. per 100 c.c. of blood; average hemoglobin coefficient, 17.8 corresponding to an average color index of 1.0; average volume coefficient, 46, corresponding to a volume index range of from .79 to 1.2; and the average saturation index, 1. They also found that the cells of newborn infants are larger and contain more hemoglobin than those of older persons but that the corpuscular hemoglobin concentration is similar to that of adults.

CLASSIFICATION OF ANEMIAS

In order to facilitate a brief review of this subject, anemias of infancy and childhood can be classified into two major groups as follows:

1. Inadequate supply, absorption, or utilization of some essential nutrient or mineral resulting in deficient red blood cell formation; namely, the so-called deficiency anemias.
2. Those from hematopoietic dysfunction. The following classification is modified from that proposed by Kugelmass[2] and will serve as a guide to a discussion of the anemias of infancy and childhood not marked by hemorrhage or jaundice. (Those anemias which are characterized by hemorrhage or jaundice and which are included in the following classification will be discussed only briefly.)

A. Deficiency anemias

I. Iron deficiency anemias

a. Prematurity type

b. Infantile type

From the Department of Pathology, Emory University School of Medicine, Emory University, Ga., and the Henrietta Eggleston Hospital for Children, Atlanta, Ga.

c. Childhood type
d. Adolescent type
e. Alimentary type
1. Celiac disease
2. Diarrheas and dysenteries
3. Intestinal parasites
4. Other gastrointestinal disorders

II. Vitamin C and D deficiency anemias

III. Thyroid deficiency

IV. Erythropoietic deficiency anemias
1. Goat's milk anemia
2. Pellagrinous anemia
3. Dimorphic anemia of malnutrition
4. *Diphyllobothrium latum* anemias
5. Gastrointestinal disorders
6. Hepatic anemias

B. Dyshematopoietic anemias
1. Congenital hypoplasia
2. Infectious aplasia
3. Chemical aplasia
4. Leucoerythroblastic anemia
5. Primary tumor anemias
6. Splenic anemia (Banti's syndrome)
7. Hepatic anemias
8. Nephritic anemias

THE DEFICIENCY ANEMIAS

Nutritional anemias of early infancy may be associated with an inability to retain the water-soluble vitamins, iron, and iodine carried over from the maternal circulation. Therefore, one infant may develop a deficiency anemia with a limited food intake early in life, while another may be protected by congenital reserves.[2] Also, the hematopoietic system must be adequately nourished for continuous generation of normal blood cells indispensable for life. In addition, the body is not dependent for its supplies of hematopoietic nutrient upon food ingestion but also upon the principles digested and absorbed in the intestinal tract. Therefore, disturbances in gastrointestinal function may predispose to deficiency anemias even if the diet is adequate. Furthermore, liver disease may enhance the development of deficiency anemias by interfering with the storage of iron and the hematopoietic factor. In addition, the toxemias of chronic nephritis, infectious diseases, lead poisoning, hypothyroidism, and allergy all prevent proper utilization of properly digested and absorbed foodstuffs. In contrast to this, one must also remember that greater nutritional requirements are necessary during muscular activity, prolonged infection, rapid growth, and

hyperthyroidism and, therefore, during these occasions failure to supply the increased nutritional needs may also lead to a deficiency anemia.

In infants and children the hematopoietic reactions to stimuli are more severe, rapid, and embryonic than in adults. The erythron of children is more immature and widely scattered, and the threshold of cellular delivery is more delicately balanced. The immaturity of the erythron renders it more susceptible to anemia-producing factors in some instances, while in others it is more resistant to such factors. Normal children seem to be born with sufficient liver storage of the hematopoietic factor for the normal maturation of red cells. On the other hand, the demands of the rapidly growing infant concomitant with the change from embryonic to extrauterine activity often predispose the child to an anemia of the deficiency type unless the food intake, especially iron, is sufficient to meet these demands.[3] Hypochromic or iron deficiency anemias therefore include those in which the hemoglobin is reduced much more than is the red cell count. This is due to the fact that the majority of the red corpuscles making up the blood in these instances are smaller than normal and are poorly filled with hemoglobin.

Prematurity Type of Anemia.—Although anemia of premature infants is a common hematologic entity, it is still the subject of much controversy with respect to its etiology. According to Windle and his associates,[4] the erythrocyte count and hemoglobin level at birth are unaffected by early or late tying of the umbilical cord. However, a difference was soon observed, and throughout the first week of life the average hemoglobin level of infants whose cords were tied late was 22.1 Gm. per 100 c.c. in comparison to a value of 19.5 Gm. in the case of the infants subjected to early tying of the cord. The actual lowering of the hemoglobin from the deprivation of placental blood as seen in a group of twenty-eight infants from 8 to 10 months of age was slightly greater than 1 Gm. per 100 c.c. of blood. Windle therefore reached the conclusion that deprivation of placental blood may be an important factor in the development of iron deficiency anemia during the first year of life and condemned the practice of clamping the umbilical cord before pulsations have ceased. Strong[5] defined the anemia of prematurity as a physiologic anemia of an infant with an impaired anatomic and physiologic development and expressed the view that lack of iron is not a factor in its causation. However, Josephs[6] states that "The anemia of prematurity, while clearly associated with iron deficiency, is also associated with other factors of importance, namely, constitution as well as repeated infectious and nutritional deficiencies."

This type of anemia is most marked at the third month when the ordinary physiologic reduction of hemoglobin is maximal. Usually the birth weight and severity of the anemia are inversely proportional to each other. If the anemia persists, it is thought to be associated with an iron deficiency, but prophylactic administration of iron does not prevent the anemia and no treatment may be concomitant with a spon-

taneous remission. In addition, the inadequacy of the hematopoietic organs, especially the liver and spleen, whose activity is more obvious during the last three months of pregnancy, may account for the obvious discrepancy between blood supply and demand. Furthermore, Sanpaolesi[7] considers that a disturbance of the mechanism of water regulation with consequent dilution of the blood is an important factor in the production of a relative anemia in premature infants. On the other hand, a number of workers attribute the anemia of premature infants to the original low total blood volume. They assume that the products of the destruction of blood are the source of materials for new blood formation until the time when the diet of the infant furnishes such substances.[8] This view becomes plausible when it is considered that the growth rate of premature infants is more rapid than that of full-term infants and that the quantity of blood must likewise be increased rapidly.

Some workers have proposed a physiologic basis for the anemias of premature infants such as the sudden change from the low oxygen tension environment in utero. Finally, in certain cases other factors may be important, and infection, particularly syphilis, is probably the most frequent. Clinically, the anemias of prematurity are characterized by marked pallor of the skin and mucous membranes. Occasionally there is splenomegaly but no hepatomegaly or lymphadenopathy. A gradual return of the blood picture to normal usually occurs after the third month unless excessive anorexia, poor diet, etc., prolongs the anemia into later infancy. Hematologically the number of red blood cells and hemoglobin levels are reduced, the latter to values less than 50 per cent, thus producing a color index of less than 1. There may be a slight reticulocytosis with presence of immature cells of the erythrocytic and myelocytic series in the peripheral blood. In general, the white blood count varies little, if any. Failure of an incompletely developed hematopoietic system to utilize iron or to synthesize hemoglobin has been suggested as the cause of anemia of prematurity. The bone marrow of premature newborn infants has been found to contain a greater percentage of normoblasts in relation to leucocytes than that of full-term newborns.[9] An entirely normal appearance of the blood as compared with that of full-term normal infants usually is not attained until 1 year of age. Many authors have considered prophylaxis in the form of repeated transfusions, although prematurity anemia is rarely severe enough to warrant such treatment. In addition to vitamins A, C, and D, saccharated ferrous carbonate (60 gr. daily) has been suggested alone or in combination with liver after the first week in life. It must be borne in mind that there is a slight refractory phase at the height of the anemia, but this gradually passes and a response in hemoglobin occurs in due time.

Infantile Type of Anemia.—Although a certain degree of anemia may be regarded as physiologic during the first month of life due to increased destruction of red cells (so-called physiologic anemia of the

newborn infant), continuous fall of hemoglobin level and erythrocytes, more frequent after the fourth month of life, must be attributed to an inability on the part of the hematopoietic tissues to meet increasing demands for blood formation. This is borne out by the experimental work of Abderhalden,[10] who demonstrated that the iron content of the liver and spleen is highest at birth and decreases gradually until the end of the normal lactation period. He and other investigators also produced an anemia in animals by continuing a milk diet for a period longer than usual.

Several etiologic factors must be considered in a discussion of nutritional anemias of infancy. First, the storage of iron by the fetus during the last trimester of pregnancy is insufficient if the mother has been anemic during pregnancy. Although Windle[4] found no correlation between the incidence of maternal and infants' anemia and although his findings were corroborated by Cunningham[11] in a study of 277 healthy infants living in the suburbs of Sydney, Australia, Bethell and his associates[12] disagree with them in that they have reported iron deficiency anemia during the first year of life in the majority of infants born of mothers suffering with untreated hypochromic anemia during pregnancy. Second, the building stones for new blood formation may be used up if new materials are not furnished in the diet. Both human and cow's milk possess a low iron content, the breast milk containing 0.5 mg. per cent. As cow's milk contains less than this, it follows that artificially fed infants will tend to show lower hemoglobin curves than wholly breast-fed infants. Third, rapid growth of the infant definitely plays its part in the production of anemia. Mackay[13] has observed that infants with lower birth weights tend to have lower hemoglobin values as they develop. In other words, the baby with the lower birth weight is growing more rapidly and will therefore show a greater demand for new blood formation than the heavier and more slow-growing infant. Occasionally gastric hypoacidity of infants[14] associated with poor absorption of ingested iron and infectious states associated with anorexia and possibly marrow depression may cause instances of infantile anemia. In fact, according to Abt,[8] the anemias that are caused by and accompany upper respiratory disease are probably the most common encountered in young infants. Anemia in these mild infections is usually slight and will be corrected quickly as soon as the infection is cleared up. However, a succession of colds or upper respiratory infections may produce a more severe anemia, the anemia in turn aggravating the infection through lowered resistance of the infant, rendering him more susceptible and the infection more difficult to clear up. It should also be noted that it is only after the baby is afebrile and on the way to recovery from his infection that therapy will be effective. Cunningham,[11] in his study of 277 healthy infants, found evidence of nutritional anemia in 7.6 per cent.

Clinical and hematologic features of this anemia have been described in detail by Parsons and Hawksley.[15] The infant may appear normal in size and weight and the degree of pallor is variable. Mucous membranes are pale, although in rare instances the skin may exhibit a dusty grayish or waxy yellowish hue characteristic of idiopathic hypochromic anemia of adults. Koilonychia (spoon nails) are also occasionally seen. Systolic murmurs may be heard over the precordium, and if the anemia is severe, definite cardiac dilatation with evidence of congestive failure may occur. The spleen is also mildly enlarged, but the lymph glands are not involved. The red cell picture is characterized by hypochromia and microcytosis. In mild cases the red cell count may not fall far below normal, but in the more severe types there may be a more marked reduction of both red cells and hemoglobin and a low color index. Platelets are normal or slightly diminished in number. The white cells tend to become increased so that a relative lymphocytosis (70 per cent or more) exists unless infection supervenes.

Mackay[16] has shown that nutritional anemia between the fourth month and the fourth year can be prevented by adequate prophylaxis which may be accomplished to a limited degree by providing the pregnant mother with adequate iron. Treatment of the nursing mother with iron is of little benefit, since such a procedure does not appreciably increase the quantity of iron in the breast milk. Furthermore, if on artificial milk feeding, suitable modification with vitamin supplements and semisolid food may prevent the development of anemia. However, the routine administration of iron directly to the baby is considered the best prophylactic measure. The dosage is 4.5 gr. of ferric ammonium citrate daily, beginning about the second month and continuing until the child is from 12 to 18 months old. The iron mixture is given gradually, requiring about one week to reach the full dose. This procedure usually prevents the development of colic and intestinal symptoms which frequently occur when large doses are given to infants too suddenly. A mixture is given to a breast-fed baby, but a combination of dried milk and the iron salt may be given to a bottle-fed baby. Larger doses of ferric ammonium citrate (from 9 to 15 gr. daily) are administered in the treatment of an infant with a proved case. However, ferrous sulfate (4½ gr. daily) gives a more rapid response, but oxidation of this preparation must be prevented to insure its therapeutic potency.

Childhood Type of Anemia.—Primary disease of the erythron is extremely rare at school age. The vast majority of the anemias of this period are symptomatic and due primarily to interference with hemoglobin formation. This anemia is usually mild in type and is associated with unbalanced diets, unhygienic surroundings, or recurrent infections. Included in the latter may be rheumatic fever associated with exacerbations of tonsillitis, joint pains, and mild chorea. Less commonly, tonsillar and dental sepsis and latent tuberculosis may have to be considered. Restrictions of diet imposed by the exigencies of war-

time have raised the question, particularly in England, of the incidence of anemia attributable to iron deficiency. A survey of 1,074 women and children, residents of London and English rural areas, was conducted by Mackay, Dobbs, Wills, and Bingham.[17] The age range of the children was from 6 months to 18 years. The findings when compared with the results of surveys made prior to the war indicated a decrease in the hemoglobin, presumably attributable to wartime diets deficient in protein and iron. In a similar study, Davidson and others[18] determined the hemoglobin level of 831 infants, preschool, and school children of working-class families living in Edinburgh, Scotland. The same type of investigation had been carried out in Edinburgh before the war. The authors found that after three years of wartime restrictions no change in hemoglobin levels had occurred in infants, but that a decline was observed in older children. They concluded that during peacetime the chief factor influencing nutrition is the economic status of the family but that in wartime food rationing and the difficulties of obtaining unrationed foods are the most important factors, irrespective of income.

If the anemia is severe, it usually means that there is some serious underlying disorder. Older children do not exhibit marked symptoms of anemia until 50 per cent hemoglobin or lower is reached. Clinically, these patients are characterized by pallor of the palms, spongy yellow mucous membranes of the lips and oral cavity, soft systolic precordial murmurs associated with tachycardia (pulse rate markedly increased by exercise with no corresponding decrease after rest), and occasional splenomegaly. Hematologically, the red blood cells may fall to a 2 to 2½ million level with from 20 to 30 per cent hemoglobin and a correspondingly low color index. Of particular interest is a case of achlorhydric hypochromic microcytic anemia in an 8-year-old child reported by Dacie and Ellman.[19] This child appeared to be perfectly healthy except for a pallor first noted at 18 months of age. The occurrence of this type of anemia in late childhood associated with achlorhydria is very unusual. Although the response to iron therapy was very satisfactory, the achlorhydria persisted after the blood count had become normal.

Treatment consists mainly of fairly large doses of iron daily (from 10 to 20 gr. ferric ammonium citrate or 5 gr. ferrous sulfate three times daily mixed with syrup to prevent oxidation). Since an adequate diet is more effective for prevention than for the cure of hypochromic anemia, many foods have been investigated for mineral content. Haydak and his associates[20] have found that, in addition to such foods as egg yolks, beans, peas, whole wheat, oatmeal, spinach, beef, and prunes, dark honey contains both iron and copper and therefore was valuable for hemoglobin formation. They used laboratory rats and fed two series, one on a diet of raw whole milk supplemented with 20 per cent dark honey. The control group received milk to which 10 per cent sucrose or light honey was added. They concluded from the rise in hemoglo-

bin in those in the dark honey group and the decline of hemoglobin in the control group that dark honey is valuable in prevention and cure of nutritional anemia in rats.

Adolescent Type of Anemia.—This type of iron deficiency limited almost entirely to adolescents is no different from hypochromic anemia occurring at other ages. Usually known as chlorosis, the disease in the older literature occupied many pages of the clinical textbook, but it is seldom seen now. This is thought to be because of better nutrition in modern diets. However, continued prevalence of milder forms of the disease is always encountered in practice with adolescents, since its cause depends upon conditions universally present. So far as can be determined, the older cases of chlorosis with extreme degrees of hypochromic anemia and green pallor in young women were brought on by defective diets and achlorhydria coupled with chronic blood loss of excessive menstruation. The disease is characterized by symptoms of profound anemia with marked weakness, dyspnea, irregularity of menses, various vasomotor disturbances, and a peculiar green color of the skin from which it derived its name. The importance of excessive menstruation in young women in producing anemia has probably been overemphasized unless the bleeding is profuse. In studies of 300 young college women, we have found no relation between hematologic values and the amount of menstrual flow. A group of sixteen women who used an average of twenty-two sanitary pads daily for from six to eight days were found to have hematologic values equal to the larger group with normal menstrual flow. Furthermore, hypochromic anemia also occurs in adolescent boys in the presence of extreme dietary restriction, excessive blood loss, or profound digestive disturbances with all characteristic manifestations except the greenish color of the skin.

Schwartzman,[21] in a scientific study of 934 high school adolescents, evaluated pallor as a screening index of anemia. He found that in 106 cases of pallor, only twenty-two had true anemia while eighty-four had pseudoanemia. On the other hand, eighty-four patients with true anemia had no clinical pallor and anemia would not have been detected without a blood count. The blood picture in chlorosis is one of extremely marked hypochromic anemia with very low color index. Red blood cells are definitely microcytic, and a leucopenia of granulocytic cells often occurs. It is quite possible that the old chlorosis might be identical with the disease seen in older women today known as idiopathic microcytic hypochromic anemia. It responds to the administration of large doses of iron (15 gr. of ferrous sulfate daily) just as do other types of hypochromic anemia. A form of familial microcytic anemia refractory to all forms of therapy employed is reported by Strauss and associates.[22] The disorder was observed in six members of an Italian family. There was no evidence of increased hemolysis; the resistance of the red cells to hypotonic solutions of sodium chloride was greater than normal, and no increase of serum bilirubin or urine uro-

bilinogen was observed. The red cells were small, and the mean corpuscular hemoglobin was nearly normal. Strauss and associates believed that the anemia was inherited as a Mendelian dominant.

Deficiency Anemias of Alimentary Type.—

Celiac Disease: Various workers have attributed the celiac syndrome in infants and young children to a disturbance of the metabolism of either fat or glucose, but there is agreement now that the difficulty is faulty absorption rather than digestion or subsequent metabolism of food substances. The clinical varieties in adolescents and adults are known as sprue. In fact, according to Hawes,[23] celiac disease, idiopathic steatorrhea, and nontropical and tropical sprue are included as one entity. It is found more frequently soon after the first year of life, following a latent prodromal period, and is characterized clinically by a recurrent diarrhea, abdominal distention, muscular debility, nutritional dystrophy, and arrested growth. Although gastrointestinal function appears normal, the impairment of absorption soon leads to an iron deficiency type of anemia. Recently, McKhann, Spector, and Meserve[24] were able to demonstrate in a number of patients with celiac symptoms some evidence of gastrointestinal allergy, as indicated by scratch or intradermal sensitization tests. They also found cases of gastrointestinal allergy which simulated very closely those of celiac disease. The added observation that absorption from the gastrointestinal tract of a fat-soluble substance, vitamin A, may be impaired in conditions known to be due to allergy but in which gastrointestinal symptomatology is minimal suggests that degrees of impairment of absorption may occur on an allergic basis. In a number of the cases studied by McKhann and his associates, the absorption of vitamin A showed a definite increase after elimination from the diet of the offending food.

Hematologically, there is a reduction of both red blood cells and hemoglobin leading to a low color index. Anisocytosis and microcytosis are characteristic. According to Hawes,[23] anemia is most prominent and may assume an aplastic, erythroblastic, hypochromic or a macrocytic, hyperchromic form. In some patients, steatorrhea is indistinguishable from pernicious anemia, and in others the blood picture may change from hyperchromic to hypochromic and from macrocytic hyperchromic to hypochromic. The cause of these changes is unknown, but the tendency is for the hypochromic variety to become macrocytic and hyperchromic as the disease advances, especially if the diarrhea persists. There may be a normoblastic reaction in infant's marrow during early stages, a megaloblastic reaction in childhood marrow during later stages, or even an aplastic reaction in patients with severe untreated cases. The easier digestion and absorption of protein therapeutically necessitates a diet largely of proteins and monosaccharides. Vitamin A and other vitamins are also given, with large doses of iron, especially in the

early stages of the disease, as encountered in infants and young children. Under treatment with liver or liver extract, hyperchromic macrocytic anemia often changes to hypochromic anemia. If, then, large doses of iron are given, the blood picture returns to normal. According to Abrahams,[25] reporting a case of idiopathic steatorrhea, administration of a low fat diet, autolyzed yeast (marmite), pills of ferrous carbonate (Blaud's pills), calcium lactate, vitamins A and D, and transfusions of blood resulted in recovery of the patient.

Diarrheas and Dysenteries: The gastrointestinal disorders such as bacillary dysentery and ulcerative colitis associated with rapid peristalsis usually cause hypochromic anemia due to chronic hemorrhage, inadequate food intake, diminished absorption, excessive elimination, and bone marrow hypoplasia. In addition, upper respiratory tract infections such as middle ear infections and streptococcal sore throat are known to produce depression of gastrointestinal tract secretions in infants, with subsequent diminution of iron absorption. Associated vitamin deficiencies may also play a part. Macrocytosis is said to develop in infants with the more severe cases of some diarrheas. The treatment of the anemia depends upon the underlying condition plus the associated hematologic picture. For example, an outbreak of chronic gastroenteritis with associated diarrhea, giddiness, malaise, anorexia, headaches, epigastric discomfort, and a moderate to marked hypochromic anemia was seen in an evacuee nursery home.[26] Infection with *Giardia lamblia* was found in 82 per cent of the school children who had a history of intermittent or continued loose stools. In practically all cases a five-day treatment of atabrine hydrochloride, from ¾ to 1.5 gr. (depending on age, size, and weight), three times daily resulted in symptomatic cure.

Intestinal Parasites: Helminths are not responsible for a large per cent of the hypochromic anemias found in children in the temperate climates, although Brown and Otto[27] made a study of the relation of anemia to hookworm infections in children from 6 to 14 years of age living in the rural counties of North Carolina and found that 42 per cent of anemic children were infected. In these cases the hypochromic anemia was usually caused by toxic substances and chronic hemorrhage produced by the parasites in addition to inadequate nutrition. Clinically, it is characterized by weakness, fatigue, palpitation, and dyspnea due to the chronic, marked, prolonged anemia and intoxication. Occasionally, dermatitis, physical and mental retardation, edema, pallor, and abdominal distention occur. Stool examination with finding of ova establishes the diagnosis.

The blood picture is characterized by the severe hypochromic microcytic anemia associated with a color index around 0.5 and absence of any active blood regeneration. There usually is a high blood eosinophilia, sometimes as high as 90 per cent in some patients with acute

cases. According to Heilig and Visweswar,[28] anemia from hookworm disease improved so quickly and regularly on iron medication (Blaud's pills—90 gr. a day) without any additional treatment and before deworming was performed that any delay in achieving this favorable response must be traced to some other active pathologic process coexistent with the ankylostomiasis. They found that such diseases as malaria, urinary tract infections, and silent middle ear and sinus infections were usually responsible for any lack of response to iron. They also stated that no calcium tetrachloride or tetrachlorethylene should be administered to a patient with a hemoglobin level below 40 per cent (Sahli), since to do so is to invite disaster. Tetrachlorethylene, when given, is used in doses of from 1.5 to 2.5 c.c. to be preceded or followed by magnesium sulfate or sodium sulfate solution in appropriate quantities.

Other Gastrointestinal Disorders: Hematopoietic problems arising postoperatively in surgery of the gastrointestinal tract are not seen as often in children and infants as in later life. Removal of the acid-bearing and intrinsic factor stomach areas must be considered when specific surgical situations are confronted. It was formerly thought that iron absorption might be seriously affected. However, data accumulated by Arrowsmith and Minnich[29] indicate that absorption occurs just as readily from the duodenum as from the stomach and even to a small degree, from the jejunum and ileum.

Congenital hypertrophic pyloric stenosis and intussusception prevent the utilization of blood-building substances and result in hypochromic anemia. Hawksley, Lightwood, and Bailey[30] reported two instances of iron deficiency anemia responding to therapy associated with an intestinal polyp unexpectedly discovered at autopsy. They also found a similar anemia in a case of ulcerative colitis. Furthermore, the tendency to treat gastrointestinal disease preoperatively and postoperatively with bland diets ignores the limited hemoglobin-producing qualities of such regimes and invariably aggravates any associated anemia. Gastric and duodenal ulcers may occasionally be responsible for hemorrhage sufficient to produce anemias.[6] These are found mainly in the marantic babies and are also associated with infection. In melena neonatorum, the bleeding has, in a number of instances, been associated with gastric or duodenal ulcers.

VITAMIN C AND D DEFICIENCY ANEMIAS

In adults suffering from scurvy, anemia is a common complication, and the vitamin C deficiency is thought to be responsible for it. However, according to Abt,[8] scurvy in infants is not constantly associated with anemia. The question of relationship of vitamin C deficiency to iron metabolism and iron deficiency in hypochromic anemia has been reopened recently in two papers. For example, Lozner[31] observed five

persons with presumptive vitamin C deficiency as evidenced by absence of or reduced ascorbic acid in the blood plasma. Three of the patients exhibited clinical signs of scurvy, one suffered from pellagra, and one had idiopathic hypochromic anemia. The diet supplied during the period of observation was low in vitamin C and vitamin B complex. In four of the patients hemoglobin increases occurred spontaneously or in response to iron medication. The authors concluded, therefore, that hemoglobin regeneration may occur in the absence of ascorbic acid in the blood plasma, as determined by chemical tests. Furthermore, Liu and associates[32] conducted a survey of 238 Chinese boys between the ages of 11 and 20 years who were inmates of a municipal institution. Over one-half of the subjects were anemic, and sixteen boys suffering with anemia were studied in detail. Eight of these were given 50 mg. of ascorbic acid daily for four weeks. The other eight boys received 1.5 Gm. of ferrous carbonate daily for the same length of time. Although in the former group the administration of ascorbic acid was accompanied by an increase in plasma content of ascorbic acid from an average of 0.23 to an average of 0.91 mg. per 100 c.c., no effects were observed either on the hemoglobin content or the hematocrit reading. In the latter group the institution of iron therapy was followed in most cases by a significant increase in red cell count, hemoglobin content, and hematocrit reading, although the subnormal readings of the plasma ascorbic acid persisted unchanged. These authors concluded that whereas anemia is commonly associated with vitamin C deficiency, the first-named disorder is, in all probability, due to a concomitant deficiency of iron.

Clinically scurvy is characterized by a generalized malnutrition, marked pallor, bleeding gums, and various other types of hemorrhages. Subclinical scurvy is characterized by a chronicity of symptoms, prolonged periods of ill health, gradually increasing pallor, slow and insidiously developing hypochromic anemia, and, finally, an outcropping of hemorrhages. The former clinical type usually responds to doses of liver and iron and vitamin C in the diet. The subclinical type needs usually only vitamin C in the diet. If from 3 to 10 ounces or more of orange, lemon, lime, or tomato juice after meals are refused or vomited, ascorbic acid tablets (100 mg.) may be given orally or parenterally (isotonically in the form of the sodium salt).

Anemia has been reported in rachitic infants and children by a large number of clinicians. However, there is little agreement as to its etiology. The state of affairs is well summarized in a quotation from Fuhr and Steenbock.[33] "It is probably true that severe rickets is generally accompanied by anemia. But whether this malnutrition is to be attributed to the rickets or to the malnutrition occasioned by associated errors of hygiene and diet remains to be determined." Typical of the contrasting opinions on this subject are the following reports: McDonough and Borgen[34] believe that there is no relationship between

rickets and anemia. They found that the feeding of iron salts to rachitic infants with subnormal hemoglobin values raised these figures to normal. They further observed that the administration of vitamin D did not increase the level of hemoglobin in the anemia of uncomplicated rickets. Crowley and Taylor[35] found that only the combined feeding of iron and vitamin D increased the level of hemoglobin in eighteen children with latent rickets. Finally, Fuhr and Steenbock[33] found that low calcium and low phosphorus rickets did not reduce the amount of body iron nor the rate of hemoglobin synthesis in the rat.

THYROID DEFICIENCY ANEMIA

Cretinism is believed to be associated with an iron deficiency or erythrocyte maturing factor deficiency accentuated by the underlying hormone insufficiency. There is thus marked variability in the type of anemia which accompanies hypothyroidism; for example, there may be a normochromic anemia gradually improved by doses of thyroid substances given in milk (initial dose of $\frac{1}{10}$ gr. once a day for infants and up to 1 gr. for a child). The amount is gradually increased by $\frac{1}{10}$ gr. daily until the limit of tolerance is attained, which may be as low as $\frac{1}{2}$ gr. or as high as 5 gr. daily. There may be a hypochromic anemia with or without intrinsic factor deficiency which responds to thyroid plus iron therapy. Clinically this disease is characterized by stunting of mental and physical growth associated with the presence of course features, dull expression, protruding tongue, thick lips, pasty skin, pale membranes, short extremities, and frequently umbilical hernia.

ERYTHROPOIETIC DEFICIENCY ANEMIAS

Anemias of this group are usually associated with nutritional, digestive, or liver disorders. Etiologically they may be due to lack of extrinsic factor in the diet, lack of intrinsic factor in the gastric juice, impermeability of the intestinal tract, inability of the liver to store the principle, faulty internal metabolism, or failure of the principle to be utilized by the blood-forming organs. As a group they are usually characterized hematologically by macrocytosis.

Goat's Milk Anemia.—This name was applied to a type of anemia observed particularly in Germany and Italy in infants fed on goat's milk exclusively. It is often characterized by chronic diarrhea and seen in poorly nourished, underdeveloped babies. It is believed that this anemia is caused by the same essential etiologic factors as those in cow's milk anemia. Recently the idea has been advanced that a deficiency of the extrinsic factor present in liver and yeast might be responsible for this condition, since hematologically it is a macrocytic anemia associated with peripheral megaloblasts and some thrombocytopenia and leucopenia. This factor is also a component of vitamin B complex. While goat's milk is not entirely lacking in this extrinsic

factor, this anemia may be cured by increasing the amount of goat's milk ingested.[36] The fact that this anemia can be cured by liver or yeast and not by iron points to the deficiency of vitamin B complex as a factor in causing goat's milk anemia. Curiously enough, according to the observations of Vollmer and Melde,[37] anemia produced in rats by a diet of goat's or sheep's milk could be lessened or entirely corrected by the addition of carrots to the diet of the milk-producing animal.

Pellagrinous Anemia.—Pellagra occurs in many parts of the world in those areas where there is intense radiation from sunlight. It occurs in the United States endemically in the southern states and sporadically in the northern states as the result of deficient diet. The disease is seen in its most characteristic form in children of poor populations whose staple diet is maize, or is otherwise poor in protein and vitamin content, being particularly low in lean meat, milk, cheese, eggs, and butter. Food fads, faulty diet, and diseases of the alimentary tract associated with diarrhea and poor food absorption are common predisposing or precipitating factors in sporadic cases in the temperate zone. The symptoms vary widely from the mild cases to severe. In general, they involve four systems, including the skin, the gastrointestinal tract, the neurologic system, and the blood. Skin manifestations consist of symmetrical areas of erythema, vesiculation, and exfoliation, with varying degrees of pigmentation occurring usually in those areas exposed to sunlight. The areas most often showing these changes are the dorsal surfaces of the hands and forearms. Gastrointestinal symptoms include sore tongue and glossitis, loss of appetite, abdominal discomfort, and, in severe stages, prolonged and diffuse diarrhea. In general, they are quite similar to those observed in sprue but the stools are not characteristic, however. Neurologic findings may be the outstanding feature, particularly the mental changes. These range from irritability, melancholia, and depression to violent maniacal outbursts. In addition, there may be various paresthesias of the hands and feet and signs of ataxia. The findings of the blood are not always those of macrocytosis and hyperchromia. In some patients the red blood cell picture is one of normocytosis and hypochromia. The volume and color indices are usually above 1, and signs of active cellular regeneration are seldom observed. Occasional leucopenia is seen, and achlorhydria is seen in less than 50 per cent of the patients, and in some of these it is corrected after adequate treatment.

Although individuals with pellagra usually have a multiple vitamin deficiency, treatment should consist in adequate amounts of nicotinic acid and an adequate diet rich in proteins. Nicotinic acid is given orally in 100 mg. doses twice daily and parenterally in 10 mg. doses four times daily. Yeast is given in 10 Gm. doses dissolved in milk or fruit juices during or between meals. Liver extract is also given to assure absorption and utilization in 5 c.c. intramuscular doses daily.

If the hemoglobin is low and the color index below normal, ferrous salts can be given by oral administration. After proper treatment the macrocytic anemia and other hematologic deficiencies are no longer present. Glossitis disappears, other symptoms rapidly improve, there is a return of hydrochloric acid to the stomach, a sense of improved well-being, and usually complete restoration to health. A comprehensive survey made by Harris and Harris[38] of the genesis of pellagra, pernicious anemia, and sprue reveals that these three diseases are not different manifestations of the same disease but three separate entities. It was conceded, however, that the three appeared to be allied nutritional disorders. They also state that if the dermatologic manifestations of pellagra are absent, then this disease, sprue, and pernicious anemia, as manifested in oral and gastrointestinal symptoms, are indistinguishable from one another. The authors also maintain that pathologic changes of the liver, usually fatty degeneration, are almost constant findings in pellagra, in pernicious anemia, and, to a lesser extent, in sprue. Atrophy of the stomach and intestines may be found in all three diseases. When changes are present in the spinal cord in any of these diseases, the lateral and posterior columns are involved. According to them this coincidence suggests common etiologic factors.

Dimorphic Anemia of Malnutrition.—According to Trowell,[39] "The war is leading to a reduction of substances rich in extrinsic factor, and cases of nutritional macrocytic anemia, with perhaps varying degrees of iron deficiency, will probably be seen in Great Britain and certainly on the Continent. Little is known about the composition of extrinsic factor except that it is present in deep muscle and probably all forms of animal protein also closely related to vitamin B complex in yeast and marmite." Clinically, there may be no symptoms but more frequently there may be slight fever and splenomegaly, which may or may not be painful. Frank anemic signs follow added other strains, such as malaria or hookworm infections. Diarrhea, sore tongue, dysphagia, leg edema, low blood pressure, and increased pulse pressure are also seen. The nails and hair are normal unless an iron deficiency is also present. The tongue never shows loss of papillae. Jaundice is absent or slight. The van den Bergh reaction is indirect, and there is an increase in serum bilirubin in some instances. The liver is also enlarged and tender and the urine contains urobilinogen. Paresthesias are common but no palsy or loss of sensation is seen. Although neutropenia is often present, severe necrotic ulcerations of the throat are quite rare.

Hematologically the red blood cells may be 1,000,000 per cubic millimeter or less, with most patients showing a color index of over 1, and, if below 1.0, there is usually an associated iron deficiency. No macrocytosis is seen, but the mean corpuscular volume is increased and spherocytic nucleated red blood cells are seen in the peripheral blood. The total leucopenia is usually due to neutropenia, and there is also a re-

duced platelet count with tendency to bleed easily. The color index and mean cell diameters used as pointers by hematologists to separate the two well-known deficiency anemias fail when microcytosis mixes with macrocytosis and hyperchromia with hypochromia. Bone marrow is hyperplastic in all long bones, and free hydrochloric acid is usually present in test meals.

Treatment of this symptom complex consists of sufficient meat (or rice polishings and green vegetables), liver extract, or yeast preparations. The term dimorphic anemia is used since two deficiencies play a part; that is, the blood smear shows a dimorphism between the central and peripheral parts of the smear. The sternal puncture reveals two deficiency types of erythropoiesis, and two factors are necessary in its treatment. With treatment, the spleen shrinks, the mean corpuscular volume falls, and the mean corpuscular hemoglobin concentration rises to normal.

Diphylobothrium latum Anemia.—Almost any type of infestation with intestinal parasites is accompanied by anemia. Apparently there is only one parasite, the fish tapeworm, or *Diphylobothrium latum*, that produces a macrocytic hyperchromic type. Birkeland[40] states that the anemia is indistinguishable from pernicious anemia clinically and the rarity of pernicious anemia in children is well known. Therefore, hematologically and not pathologically the two may be related. The infection occurs mainly in this country among Finns and their children. It has also been observed in Jewish people in Brooklyn[6] but has not been associated with anemia in these people. Birkeland further points out that achlorhydria is present in 84 per cent of the patients, that the anemia is usually cured after the expulsion of the worm, but that the presence of the worm is not the only factor in the production of the anemia. Therefore, he believes that the fish tapeworm infection is only the precipitating factor producing the anemias. Furthermore, the fish tapeworm may directly or indirectly enlarge the intestinal wall so the toxins may be absorbed and act directly on the blood-forming organs. Therefore, it would appear from Birkeland's review that the fish tapeworm is the precipitating factor producing the pernicious anemia-like blood picture in the person who is already susceptible to the disease. This is supported by the fact that only one out of 5,000 people, including children with the infection, develop the characteristic anemia. Therapy consists mostly of antihelminthics and liver extract parenterally. Two cases of macrocytic anemia have also been observed in association with infection with the beef tapeworm, *Taenia saginata*, and one seen in association with the round worm, *Ascaris lumbricoides*.[41]

Other Gastrointestinal Disorders.—Other gastrointestinal disorders include diseases of the alimentary tract in which dietary lack of the extrinsic factor, deficiency of the intrinsic factor, or faulty absorption, or storage of certain erythrocytic hemoglobin-forming principles are

seen. Such diseases include celiac disease, intestinal narrowing, with or without complete obstruction, dysentery, and colitides singly or in combination. In addition, postoperative states involving loss of intrinsic factor-forming regions of the gastrointestinal tract may be responsible. Of further interest are cases of macrocytic hyperchromic anemia in infancy reported by Fouts and Garber[42] and by Cole.[43] This type of blood dyscrasia in infancy is usually observed in previously healthy infants after an infection of the upper respiratory tract followed by a period of vomiting or diarrhea or both. Patients are noticeably malnourished and fail to gain weight in spite of changes in formulas and additions of various vitamins to the diet. Free hydrochloric acid is nearly always present in the gastric content, although frequently decreased in amount. The administration of crude liver extract by mouth or injection is usually followed by reticulocytosis and a rapid rise in the number of red blood cells and gain in weight. Anemia does not recur after it has once been corrected.

Hepatic Anemias.—Diffuse involvement of the liver interferes with production and transportation of the erythrocyte-maturing factor to the bone marrow. The resulting anemia may then be normocytic or macrocytic but is usually the latter, depending on the degree of liver damage. Jaundice may or may not occur. Those anemias in which the physical signs occur will only be mentioned here for reasons previously given. This anatomic division includes cirrhosis of the liver, tumors of the liver, and Banti's syndrome. Treatment includes a high carbohydrate diet, low protein, diuresis by special drugs, ascitic control with periodic paracentesis, and intramuscular liver for the macrocytic anemia.

DYSHEMATOPOIETIC ANEMIAS

Malfunction of the bone marrow may result from primary bone marrow disease or be secondary to other systemic diseases. It should be repeated here that the food substances necessary for hematopoiesis may be adequately supplied, digested, and absorbed, but, despite all this, the blood-forming tissues of the marrow cannot utilize them. However, on occasion, the bone marrow may regenerate. If this occurs the otherwise fatty or aplastic marrow may become normal or hyperplastic. Therefore these anemias are characterized by decreased red cell formation leading to a gradual disappearance of the red blood cells from the peripheral blood. The associated leucopenia may lead to intercurrent infections, and the thrombocytopenia to hemorrhagic manifestations.

Congenital Hypoplasia.—During the past few years several reports have appeared in the literature describing a peculiar anemia occurring in early infancy. All cases described had certain features in common and did not fit into any one of the accepted classifications. The condition appeared to be one of congenital constitutional origin. Clinically it is characterized by a marked anemia with occasional hemic cardiac

murmurs, bleeding from mucous membranes; it occurs very rarely and is usually quite severe. Hematologically these cases were characterized by hypoplasia rather than an actual aplasia of the bone marrow elements. Erythropoiesis only was affected, while the leucocytes and platelets were normal or only moderately diminished in number. There was no hemorrhagic tendency. None of the commonly employed dietetic or medicinal measures produced improvement and the patients were kept alive only by repeated transfusions. Blackfan and Diamond,[44] in 1938, reported four such cases and mentioned four others, probably unreported. Rubell[45] also described a case in which bone marrow deficiency was apparently temporary in nature, since spontaneous blood regeneration, which was absent at 3 months of age, began at 21 months of age. An interesting feature of Rubell's patient was the remarkable recuperative power of the infant and his resistance to infection during periods of profound anemia.

The etiology of this type of anemia is unknown. The possibility of a metabolic disturbance involving some blood-building substance is suggested by Blackfan and Diamond. The prognosis is apparently good if transfusions are given frequently enough to tide the child over the period of bone marrow inactivity. Of course the difficulty of giving repeated transfusions to small children is obvious.

Infectious Aplasia.—Many acute and chronic infections are associated with hypoplasia of the bone marrow. These include staphylococcic sepsis, miliary tuberculosis, chronic osteomyelitis, rheumatic fever, subacute bacterial endocarditis, chronic ulcerative colitis, and others. It is thought that the marrow function becomes depressed by toxic products elaborated from the organisms or from the tissues destroyed by them. According to Bomford and Rhoads,[46] this variety of anemia may be caused by a conditioned susceptibility to toxic substances, usually exogenous or endogenous aromatic hydrocarbons (benzollike in nature). At first the marrow is hyperplastic with immature cells in the peripheral circulation. Then, gradual hypoplasia develops with associated marked diminution of the number of red blood cells, white blood cells, and platelets in the peripheral circulation. Clinically, a marked pallor, dyspnea, and occasional peripheral edema with accompanying infectious episodes and ulceration are observed. Therapy consists first in the elimination of the focus or foci of infection if possible. Kracke,[47] regarding Bomford and Rhoad's theory of absorption of benzollike compounds from the lower gastrointestinal tract as being worthy of therapeutic experiment, used large repeated prolonged sulfasuxidine medication in an attempt to sterilize the bowel and possibly prevent reabsorption of these toxic substances. Although good results have been obtained with one young male with aplastic anemia without the use of transfusions, recovery, of course, could have been a spontaneous remission. The drug has failed in other cases. Repeated small trans-

fusions have only a temporary effect and may at certain stages be harmful, leading to acute hemolytic episodes.

Chemical Aplasia.—A severe aplastic anemia may accompany the administration of certain drugs such as arsphenamine, other coal tar products, and the sulfa drugs. Poisoning with benzol and gold may also cause severe aplastic anemia. Finally, exposure to x-ray and radium may produce this type of anemia. Such anemias may clear up rapidly if the drug is withdrawn. On the other hand, the anemia may persist with great stubbornness if serious damage has been done to the bone marrow. Doan[48] emphasizes that the incidence of idiopathic aplastic anemia is becoming less as the number of known chemicals and toxins potentially depressant to the marrow increases. He names fourteen criteria for the diagnosis of this condition, including a history of exposure to toxic medicinal or industrial agents, no weight loss or anorexia, normal basal metabolic rate, hypochlorhydria, minimal adenopathy, no splenomegaly, granulocytopenia, no immature myelocytes, thrombocytopenia with purpura an early prominent sign, a normochromic, normocytic anemia, an absolute decrease in reticulocytes, a normal red cell fragility, and panhypoplasia of the sternal marrow.

In arsenical intolerance thrombocyte diminution occurs first, then granulocytic, and, finally, erythrocytic diminution. Vitamin C administration is said to increase marrow resistance to arsenic injury, although it does not prevent intolerance to the drug. Weakness, pallor, dyspnea, and palpitation are characteristic symptoms of the associated anemia. Occasionally a severe dermatitis associated with anaphylactic shock is seen in some patients. Treatment consists of repeated blood transfusions, a high carbohydrate diet, and liver preparations for liver damage. Occasionally sodium thiosulfate, from 0.1 to 0.5 Gm. intravenously given before arsenic treatment, accelerates urinary excretion of the drug. Toxic reactions with sulfa drugs may be in the form of acute hemolytic anemia associated with a previous slight rise in reticulocyte count. Leucopenia and thrombocytopenic purpura[49] are also seen as toxic manifestations of the drug. In benzol poisoning in children, oxygen inhalation, blood transfusions, liver extract, pentnucleotide and vitamin K may be helpful. Allergic susceptibility of children to gold salts is seen more often since the increasing use of this metal in whooping cough, tuberculosis, lupus erythematosus, and rheumatic arthritis. Since this drug has a cumulative action, it is wise to be aware of the early forms of toxicity; that is, diminution of lymphocytes, increase of eosinophiles with a progressive anemia, and sudden thrombocytopenia. Therapeutic measures should include 10 per cent sodium thiosulfate, intravenous dextrose, and repeated transfusions.

X-ray intoxication is manifested by digestive disturbances, progressive weakness, and extreme nervousness. The reactivity of the marrow varies in children, there being first the initial stimulating effect, to be

succeeded by the toxic effect characterized by leucopenia and finally anemia. Radiation sickness subsides in a few days and may be alleviated by nicotinic acid and thiamine in large doses. Treatment of radiation anemia is the same as that used for the aplastic type.

Leuco-Erythroblastic Anemia.—Vaughn[50] has pointed out that the red blood cell changes in leuco-erythroblastic anemia are characterized not so much by anemia as by the appearance in the blood of young erythrocytes and nucleated forms, or a shifting of erythropoiesis to the left. These changes imply that the blood picture is the result of dyshematopoiesis due to foreign tissue in the marrow which probably disturbs the nutrition of the erythropoietic tissue. This view explains the hyperplastic appearance of the marrow and enables the red cell changes to be explained in the same way as those that occur in the leucoblastic tissue; that is, because of a stimulating effect, although the stimulation causes a disordered erythropoiesis and not a simple compensatory hyperplasia.

Clinically, the symptoms are quite variable, depending on the underlying causative disease plus those associated with the anemia. Changes in the marrow cavity may cause deep bone pain and bone erosion. In addition, extramedullary sites of hematopoiesis form in the liver, spleen, or lymph nodes, leading to their enlargement with a variable microscopic picture. Hematologically the peripheral blood may resemble the leucemic or erythroblastic anemia without hemolytic phenomena. Those disorders that are thought to cause this condition include bone tumors, leucemia, miliary tuberculosis, Niemann-Pick disease, osteosclerosis, osteopetrosis, and Hand-Schüller-Christian disease. Therapy is of little use, and the prognosis depends on the nature of the systemic disease.

Primary Tumor Anemias.—Little attention is usually given to the anemia that accompanies malignant tumors of infancy and childhood mainly because it is of minor importance compared with the tumor process itself and partly because the blood changes are not sufficiently characteristic to contribute to the diagnosis of the tumor. The primary tumors most commonly encountered in infancy and childhood are neuroblastoma, renal tumors (usually Wilm's type), lymphosarcoma, and a miscellaneous group comprising sarcomas arising in retroperitoneal tissues, intestines, bones, etc. The anemia, although at first hypochromic in type, may later simulate any type of blood dyscrasia, depending on the amount of involvement of the gastrointestinal tract, liver, and bone marrow. Treatment consists in therapy of the original neoplasm.

Splenic Anemia (Banti's Syndrome).—There has been a great deal of controversy over the syndrome characterized by anemia, splenomegaly, neutropenia, and liver atrophy that has been called congestive splenomegaly. Obstruction in the liver or portal circulation is also very frequently associated with hypoplastic anemia. The disease may

occur in childhood but is not limited to any age level. In view of the claims that splenectomy is an effective remedy in some patients, particularly those without advanced hepatic damage, the pediatrician should be certain that all causes for anemia are nonexistent before a diagnosis of this condition is made. It is said that if pyogenic infections, syphilis, malaria, leucemia, thrombocytopenic purpura, hemolytic icterus, von Jaksch's anemia, Cooley's anemia, and deficiency anemias are definitely ruled out and the patient exhibits the above clinical and hematologic syndrome, Banti's syndrome may be considered a probable diagnosis.

The anemia is macrocytic and hyperchromic unless an iron deficiency results in a hypochromia. The red blood cells are large or normal in size. Volume and color indices are increased. The neutropenia may be marked, sometimes as low as from 1,000 to 2,000 cells per cubic millimeter. The platelets may or may not be decreased. Diagnosis is based on the enlarged spleen, small atrophic liver, neutropenia, macrocytic anemia, hematemesis, and other hemorrhagic episodes in some patients. Treatment is only palliative. The value of splenectomy has not been proved in all cases.

Hepatic Anemia.—Since these dyscrasias are usually caused from liver disorders and therefore frequently associated with jaundice, they will not be discussed here. Suffice it to say that the macrocytic or normocytic anemia which does occur in a variety of liver diseases is usually caused by impaired storage or disturbed synthesis of erythropoietic elements.

Nephritic Anemia.—The intractable anemia of nephritis has been extensively investigated in adults, but there has been little detailed study of the blood changes occurring in the nephritis of childhood, although at this age complicating factors are less common than in adults. MacArthur's[51] results seem to show that both in the nephritic syndrome and in acute hemorrhagic nephritis there are definite changes in concentration of certain constituents of the blood but that there is no evidence that either disease produces any absolute diminution in the number of red blood cells or in the hemoglobin content. In nephrosis the concentration reaches its height during the period of oliguria and when edema is pronounced, whereas in acute hemorrhagic nephritis it reaches its maximum during active diuresis and when edema is subsiding. Therefore, in the nephritic syndrome any anemia that may be present will be masked during increasing edema by hemoconcentration, and the true state of the blood will become evident only during a nonedematous phase. On the other hand, in acute nephritis, serial counts done when the patient is recovering and when diuresis has ceased will reveal what appears to be an increasing anemia but is, in reality, only a diminishing hemoconcentration. Not until some weeks after edema has disappeared will the red blood cell count reflect the true state of the blood. Any further reduction after this

would indicate a true progressive anemia. Contrary to the findings of other workers, MacArthur's work failed to demonstrate anemia in nephrosclerosis in the absence of such complicating factors as hemorrhage. It seems, therefore, that only in chronic glomerulonephritis is there true anemia which is normochromic and normocytic and its cause is difficult to explain. It might be suggested that the anemia in this type of nephritis is due to loss of blood through the kidneys, but this is impossible, as the amount of blood loss is extremely small and, in addition, chronic hemorrhage should lead to an anemia of the hypochromic type, and the fact that treatment with iron is of no avail provides additional evidence that it is not due to blood loss. Furthermore, it does not appear to be due to marrow aplasia for there is no diminution in the number of white blood cells, and reticulocyte counts are within the normal limits. However, sternal marrow studies should be of interest in these cases and perhaps would give a lead as to the exact nature of the hematopoietic disorder.

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BLOOD TYPING AND CRITERIA FOR BLOOD-TYPING SERUMS

WILLIAM THALHIMER, M.D.
NEW YORK, N. Y.

LANDSTEINER,[1] in 1900, published his original paper describing the human blood groups, and their practical significance.

By his methods transfusion reactions which previously were unexplained could be shown to be caused by the transfusion of incompatible blood. Even more important than this was the demonstration that the compatibility of bloods could be determined by laboratory tests before transfusion, making transfusions safe, and when the tests are accurately performed eliminating the danger of specific, incompatible reactions which, at times, may be fatal.

Hektoen,[2] in 1907, was the first in this country to point out the necessity of blood typing and compatibility tests before giving transfusions.

Ever since blood transfusions have been established as an important therapeutic procedure it has been generally agreed that the safety of transfusions must be determined by performing both typing and compatibility tests before carrying out the transfusions.

In spite of wide dissemination of this information there is still the occasional occurrence of a fatal incompatible transfusion reaction because of errors in blood typing. The commonest reasons for these errors are use of weak or unsatisfactory typing serum, and neglect to do cross-matching tests which not only determine compatibility but pick up errors if they have occurred because of poor typing serums.

Recently the Rh factor has been found to be another cause of some incompatible and even fatal transfusion reactions.

Determination of Blood Types.—In order to determine blood types it is essential that anti-A and anti-B typing serums be used which have not only high titers, but also the ability to cause rapid, clear-cut agglutination readily observed by the naked eye. Of course, a proper, careful technique is necessary in the hands of sufficiently well-trained workers.

Until recently references were made to highly titered and rapidly acting typing serums only in vague terms. Now studies made by many investigators enable us to be more specific, and it is hoped will lead to standardizing both the typing serums and the tests.

The most important qualities these typing serums should possess are the ability to cause the formation of large clumps of agglutinated cells

From the Human Serum Division of the Public Health Research Institute of the City of New York, Inc.

rapidly, to be specific for cells containing A or B substance (agglutinogens), and to agglutinate cells of the different subgroups, such as A_2 and A_2B. Errors in typing may be made with these subgroups if weak slow-acting serums are used. There is a special reason why the serums should have high agglutinin titers, as experience has shown that otherwise, on standing in the liquid state, they may lose their ability to cause rapid, clear-cut agglutination.

These characteristics can be demonstrated with the usual microscope glass slide and macroscopic (naked eye) observation. Place on the slide a drop of a 2 to 5 per cent suspension of cells in physiologic saline, and add a drop of the undiluted typing serum. Mix with the end of a toothpick, and slowly rotate the slide. With the A serum (anti-B) easily detectable, beginning agglutination should occur in not longer than fifteen seconds, and should be complete in thirty seconds. Also, and with the same technique, a 1:16 dilution of the typing serum should agglutinate the cells within ten minutes.

With the B serum (anti-A) additional tests should be made because of the weakly agglutinable cells belonging to subgroups A_2 and A_2B, etc. There are the same time and dilution requirements for group A_1 blood, but for group A_2 blood, although typing serum diluted to 1:16 must also agglutinate the cells within ten minutes, sixty seconds can be allowed for visible agglutination to be caused with A_2 cells.

All typing serums should be tested at frequent intervals with known A_1, A_2, and B cells to make certain they have not deteriorated, especially if they are kept in the liquid state. Bacterial contamination can render a serum useless and even cause it to give nonspecific agglutination. Therefore, typing serums are safer when kept in the frozen or dried state.

It is obvious that additional accuracy can be secured, and the possibility of error reduced by using two sets of typing serums in each blood-typing test. An additional safeguard would be to have these tests carried out independently by two technicians, each using a separate set of typing serums. Each technician should read his own tests and the tests of the other technician as well, record all of the readings independently, and only after it has been found that these readings check should the blood type be reported.

In order to check the typing as performed with the individual's cells, plasma or serum should also be tested for its agglutinin content by using both known A_1 and B cells. These tests are carried out as described, but using the serum or plasma with known A and B cells. Even though some individual's serum may contain only a weak titer of the appropriate agglutinin an experienced worker will always detect it, although low-power microscopic examination may be necessary to observe the weak agglutination.

In addition to these tests it is highly desirable that an accurate standardized method be used for determining the agglutinin level or titer of the typing serums. This should be a test tube method of titration, and need not be described here. Fortunately, such a method is being more and more widely used in laboratories responsible for distribution of typing serums. With such a method in general use, titrations performed in different laboratories can be accurately compared with each other, whereas, until recently, the most diverse results were obtained because widely different and not comparable techniques were used throughout the country.

Direct Compatibility Tests Between Bloods of Recipient and Prospective Donor.—It is generally agreed that not only must the blood types of donor and recipient be known, but direct compatibility tests must be made of patient's serum with donor's cells, and donor's serum with patient's cells before transfusion.

Of these two compatibility tests it is absolutely essential that the patient's (recipient) serum should not agglutinate or hemolyze the prospective donor's cells. Otherwise the transfused cells will be agglutinated and hemolyzed within the recipient's blood stream, and if enough incompatible cells are transfused before this is discovered by the patient's symptoms and response, severe and even fatal, specific, incompatible reactions will occur. However, incompatible agglutinins in the fluid part of transfused blood, or in plasma or serum, do not carry with them this danger. Otherwise the term universal donor could not have arisen, and it would be unsafe to administer universal donor (type 0) blood to type A, B, or AB recipients, since 0 blood always contains anti-A and anti-B agglutinins.

Since the cells of type 0 individuals are not agglutinable by the plasma of individuals belonging to any blood group, the only danger which could arise would be from intravascular agglutination or hemolysis from agglutinins or hemolysins for cells of recipient individuals belonging to the three other blood groups.

The question, therefore, is: Are there any universal donors with sufficiently high agglutinin titers against A or B cells who may be considered under the circumstances outlined as dangerous universal donors? Although a small number of investigators still believe that very occasional dangerous universal donors do exist, the consensus of opinion is contrary to this. However, should there be doubt in anyone's mind, and should there be time, a very simple test will determine the safety of the universal donor.

A 1:50 dilution of the donor's plasma should be made in physiologic saline, and a drop of this should be mixed on a glass slide with a drop of a 2 per cent suspension of the patient's (recipient) cells. If after mixing and rocking backward and forward from time to time over a period of ten minutes no agglutination can be seen by the naked eye,

then the agglutinin titer is not high and the donor's plasma may be used. However, if the emergency is very great one need not hesitate to use a type O individual as a donor, regardless of the recipient's blood type.

The direct compatibility tests are practically always carried out by a slide technique as described for blood typing, with observation for agglutination made with the low power of the microscope. A drop of the recipient's plasma or serum is mixed on half of the slide with a drop of a 1 or 2 per cent cell suspension of the donor's cells, and similarly a drop of the donor's plasma or serum with a drop of cell suspension of the recipient on the other half of the slide. Mix well, using the two ends of a toothpick for the two mixtures, rotate, and observe for ten minutes.

There is a still more sensitive method which should be used, especially under certain circumstances, if time permits. The mixtures, as just described, should be made in separate test tubes with equal parts of the constituents, and the test tubes should be placed in a water bath at 37.5° C. for one hour. The test tubes should be shaken gently to see if there is visible agglutination, and if not, a drop should be placed on a slide under the low power of the microscope and observed for agglutination.

It was formerly thought that it was difficult to determine the blood types of newborn infants. Now it is well recognized that the blood cells of infants belonging to types A, B, or AB are readily agglutinable with potent typing serum, even though the agglutination may be somewhat weaker than that of later life.

However, at times, the serum of very young infants may not contain demonstrable agglutinins corresponding to their blood type. Since, on this account, accurate cross-matching may be impossible it is of extreme importance, under these conditions, that the blood group of the infant and the prospective donor be determined with at least one set of potent typing serum, and preferably with two sets.

Source of Reliable Typing Serums.—Reliable typing serums can now be purchased at a number of places throughout the country. These serums are obtained from individuals who have been proved to have high-titered, quick-acting agglutinins. It is usually a long and tedious search to find these donors.

Several methods have been devised recently to increase the agglutinin content in type A or B individuals to a level satisfactory for blood typing. Witebsky[8] has demonstrated that the intravenous injection of several small doses of his mixture of types A and B substances will, in from two weeks to one month, stimulate the development of agglutinins to a very high titer. Several specimens of his serums which he was kind enough to submit have been found to have very high titers, show marked avidity, and are excellent typing serums.

Wiener[9] has accomplished the same result by the intravenous injection of from 300 to 500 c.c. of pooled plasma into individuals belonging to types A or B. This is extremely interesting, and important, because in some unpublished studies I have found that there is either no free A or B substance, or an infinitesimal amount in pooled plasma, providing there is an excess, even though a slight one, of agglutinins. Apparently all of the A or B substance is combined with the corresponding agglutinins. Wiener's studies indicate that this must be a loose combination so that the loosely combined A or B substance can stimulate the marked increase in agglutinins, as just described. This apparently is similar to the stimulation of diphtheria antitoxin by the injection of neutralized mixtures of diphtheria toxin and antitoxin.

It has been found that isoagglutinins can be concentrated by methods which have been used in the past for concentrating other types of antibodies, such as diphtheria antitoxin. Thalhimer and Myron[3] accomplished this by concentrating the globulin fractions of low-titered serum with the well-established ammonium sulfate and sodium sulfate methods. With these methods a satisfactory globulin fraction which could be used for blood typing usually, but not always, resulted.

Elliott and Pillemer took up this study, and Pillemer[4] developed an excellent methyl alcohol process which yields unusually good typing fractions. This work was then continued in the laboratory of Dr. E. J. Cohn with his chemical fractionation process, by Lt. Pillemer, Lt. Elliott, M. Melin, J. L. Oncley, and M. C. Hutchinson. Their preparations are excellent and can be produced in large amounts without having to search for individuals who will furnish unusually high-titered serum.*

Rh Factor.—Under compatibility tests it was stated that with these tests the prospective donor's cells must not be agglutinated by anti-A or anti-B agglutinins of the patient's serum. It has been demonstrated in recent years that some individuals develop under certain conditions an additional kind of intragroup agglutinin and hemolysin. Since these were discovered by Landsteiner and Wiener,[5] in a study of both rhesus and human blood, they named the common property the Rh factor. The cells of about 85 per cent of all individuals, regardless of regular blood types, contain this Rh factor, and will be agglutinated by serums sufficiently potent in anti-Rh agglutinin. These individuals are, therefore, called Rh positive, and the remaining, about 15 per cent, are Rh negative.

Anti-Rh serum can be prepared by immunizing guinea pigs with several injections of blood from Macacus rhesus monkeys. It has been found that some Rh-negative women may give birth to an Rh-positive

*These materials were prepared, from blood collected by the American Red Cross, in the Department of Physical Chemistry, Harvard Medical School, under contract with the Committee on Medical Research of the Office of Scientific Research and Development and in collaboration with the Division of Blood Research, Army Medical School. The titrations were carried out at the request of the Blood Substitutes Committee of the National Research Council.

child, who inherits the Rh factor from an Rh-positive father. During intra-uterine life the Rh-positive fetus stimulates, across the placenta, the formation of anti-Rh agglutinins in its Rh-negative mother's blood. These new agglutinins may be strong enough to cause a severe or fatal reaction to the mother, should she receive a transfusion of Rh-positive blood, even though it is compatible according to the Landsteiner blood grouping.[6] Also, these fetuses are liable to die in utero, and be stillborn, or, if born alive, may have the condition erythroblastosis fetalis, as shown by Levine and co-workers.[7] They usually die soon after birth, unless they are given one or more transfusions immediately of sufficient amounts of Rh-negative compatible blood.

It has been found that only some of these women who are Rh negative develop a sufficiently high titer of anti-Rh antibodies to be readily demonstrated. In other patients, although the anti-Rh antibodies are present and can cause severe or fatal reactions should the women receive a transfusion of Rh-positive blood they may be so weak that it might be extremely difficult or impossible to demonstrate their presence by in vitro tests. Therefore, Rh-negative women belonging to this clinical category, should they need to be transfused, should receive only Rh-negative compatible blood.

By this simple procedure one can be certain that the patient will receive a safe transfusion. This is much simpler than determining whether the patient and father of the child are Rh positive or negative, and whether the child, if one has been delivered, is Rh positive or negative. It is obvious that an Rh-positive woman cannot develop anti-Rh antibodies under any circumstances.

It has been found that some Rh-negative individuals, male or female, who have received a number of transfusions will develop anti-Rh agglutinins if some of the blood they were given was Rh positive. One should emphasize that Rh-negative children, men, or women who are not pregnant and who have never been pregnant, are equally liable to develop anti-Rh agglutinins after multiple transfusions of Rh-positive blood. Subsequent transfusions of Rh-positive blood will cause more and more severe reactions. By these reactions, warning is given the clinician, and he should heed this by using only Rh-negative donors from then on, for an additional transfusion with Rh-positive blood might produce an extremely severe or even a fatal reaction.

Tests for the Rh Factor.—Unfortunately, it is difficult to secure potent anti-Rh serum from either the mothers who have been immunized by their own fetus, or from guinea pigs immunized with rhesus blood. However, larger amounts of satisfactory serums are becoming available.

Also, tests for the Rh factor are not as simple as those for the A and B factors, and require much more experience to perform and interpret.

Nevertheless, the importance of the Rh factor is well established, and workers and technicians must be trained to carry out these tests accurately.

SUMMARY

1. Blood-typing tests should be performed only with highly-titered, rapidly acting, standardized anti-A and anti-B typing serums.

2. These typing serums should be checked at frequent intervals with known type A and type B cells.

3. The blood type of the individual should be checked by determining the type of serum or plasma with known type A and type B cells.

4. The pretransfusion tests should include direct cross-matching of patient's and prospective donor's cells and serum or plasma.

5. Pregnant or recently pregnant women who are Rh negative and need to be transfused should receive only compatible Rh-negative blood.

6. If any individual—man, woman, or child—has had or is going to need repeated transfusions, one should determine whether the patient is Rh negative or positive. If Rh negative, then additional transfusions or repeated transfusions are safer if performed only with compatible Rh-negative blood.

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JAUNDICE AND CONDITIONS ASSOCIATED WITH THIS PHENOMENON

MADELEINE FALLON, M.D.
LOS ANGELES, CALIF.

JAUNDICE is a common symptom in the newborn and young infant and not uncommon in older children. The causes are numerous; nevertheless, jaundice is produced by only three processes. These are as follows:

I. Blood Destruction
   A. Blood destruction by phagocytosis on the part of the reticulo-endothelial system
   B. Hemolysis

II. Obstruction
   A. Anomalies of bile ducts
   B. Cholangitis
   C. Obstruction in liver cells
   D. Calculi
   E. Pressure on common bile duct

III. Liver Destruction
   A. Atrophy
   B. Fatty degeneration
   C. Cirrhosis

Although at times one may find all three processes present, that is, blood destruction, obstruction and liver damage, the conditions which cause jaundice can be subdivided under these three headings as follows:

I. Blood Destruction
   A. Phagocytosis
      1. Physiologic icterus
      2. Bacteremia
      3. Infections, acute and chronic
      4. Familial icterus
      5. Erythroblastosis
   B. Hemolysis
      1. Rh reactions in transfusions
      2. Paroxysmal hemoglobinuria
      3. Malignant malaria (blackwater fever)
      4. Snake venom
      5. Poisons and drugs

II. Obstruction
- A. Congenital anomalies of bile ducts
- B. Cholangitis
  1. Infections
  2. Bacteremia
  3. Erythroblastosis
- C. Cloudy swelling of the liver cells
  1. Infection
  2. Bacteremia
  3. Erythroblastosis
- D. Calculi
  1. Familial jaundice
  2. Cholecystitis
- E. Pressure on common duct
  1. Lymph glands
  2. Tumors

III. Liver Destruction
- A. Infections
- B. Bacteremia
- C. Drugs
- D. Poisons
- E. Tumors, primary or metastatic

In order to determine which of the above processes is present, certain laboratory procedures are necessary.

LABORATORY PROCEDURES

Icterus Index.—The icterus index tells us more than the degree of jaundice. If an icterus index is 50 or below, it is compatible with a jaundice resulting from blood destruction alone. If, however, the icterus index is 75, or 200 or 400, it is absolutely certain that blood destruction cannot be the only cause of this jaundice. Obstruction in the bile passages or in the liver cells must be present to enable the bilirubin level to reach such a height.

Van den Bergh Test.—The van den Bergh test is supposed to differentiate an obstructive jaundice from a jaundice resulting from blood destruction. However, jaundice is seen in the newborn infant when there is no blood destruction, yet the van den Bergh test is indirect. The only conclusion to be drawn from such information is that the liver cells are so affected that bilirubin does not pass through the liver cells to be reabsorbed. Thus we have an obstructive jaundice producing an indirect van den Bergh test.

Blood Destruction.—To determine whether or not there is blood destruction, one studies the daily erythrocyte and the reticulocyte counts. If the erythrocytes remain fairly constant and the reticulocyte count is

not increased, there is no abnormal amount of blood destruction. If, however, the daily erythrocyte counts remain constant and reticulocytes are increased considerably above the normal level, blood destruction or loss of blood by hemorrhage is occurring. Also, if in the presence of a high reticulocyte count, one finds a constant reduction in the erythrocyte level, blood destruction or loss of blood by hemorrhage is taking place. If the reduction in erythrocytes occurs as the result of blood destruction, the icterus index will be elevated; if the icterus index is normal, it is the result of blood loss by hemorrhage.

Hemolysis.—Hemoglobinemia and hemoglobinuria are present only when there is true hemolysis of the erythrocytes. Hemoglobinemia is a rare finding in proportion to the number of anemias that are termed "hemolytic." The majority of cases of jaundice seen with anemia are not hemolytic; instead the erythrocytes are destroyed by phagocytosis in the reticulo-endothelial system. Unless free hemoglobin has been demonstrated in the plasma and in the urine, the presence of such should not be implied by the term hemolytic.

Bile Pigments.—The presence of a normal amount of bile pigment in the stool early in life rules out a complete atresia of the bile ducts. However, a slight trace of bile pigment that has been excreted from the wall of the bowel may be present in an atresia of the bile ducts. The absence of bile pigments in the stool does not necessarily mean atresia of the bile ducts. In many newborn infants jaundice is found with complete absence of bile pigment in the stool for a considerable period of time. Some of these have proved later to have had only a temporary obstruction on the basis of cholangitis or swelling of the liver cells.

JAUNDICE IN THE NEWBORN INFANT

Icterus Neonatorum.—The simplest jaundice in the newborn infant is the physiologic jaundice or icterus neonatorum. This is a mild jaundice occurring on the third to fifth day and disappearing within a few days. It entirely disappears by the tenth or twelfth day. The infant is born with a high hemoglobin and erythrocyte count. With the increased oxygen supply after birth, the need for such a high blood level has ceased. The red cells are taken out of the circulating blood by phagocytosis and are decreased from 7,000,000 to 5,000,000 within a few days. This destruction of red cells may produce an icterus index of from 30 to 50. Since there is no liver involvement, the bilirubin is rapidly excreted. Baker[1] states that physiologic jaundice has been known to remain for five weeks. Any icterus which is severe or which lasts past the twelfth day should not be considered physiologic.

Infectious Jaundice.—There are a large number of cases of jaundice in the newborn infant which have been incorrectly called physiologic icterus or prolonged physiologic icterus. These infants are jaundiced at birth or become jaundiced during the first week or later. They develop an extreme degree of jaundice with an icterus index ranging

from 75 to 400. They have no anemia and little or no blood destruction. Consequently, the jaundice can be explained chiefly on the failure to eliminate bilirubin. They are usually free of fever. They eat well and gain weight. The stools may be acholic or they may contain bile pigment. The duration of the jaundice may be from four to twelve weeks. The majority of infants so affected recover completely with no specific treatment.

In some of these infants one finds an infected cord, pus in the umbilical stump, or hemorrhage from the cord or the stump. This infection travels up the umbilical vessels to the liver and produces inflammatory changes in the liver and, in many instances, a bacteremia.

In some infants with no evidence of any definite portal of entry for a bacteremia, the blood cultures have been positive. Negative blood cultures do not rule out the possibility of a bacteremia. Neither does a normal temperature. In some patients who have had negative cultures and were fever free and have come to autopsy, evidence of infection, such as multiple abscesses, acute hepatitis, or cholangitis, has been present. Therefore in the recovered infants it seems reasonable to expect that the most likely lesions have been cholangitis or hepatitis or cloudy swelling of the liver cells.

CASE 1.—G. A., a Mexican male, was admitted to the hospital at the age of 2 days. Weight on admission was 10 pounds, 9 ounces. There had been some difficulty in delivering the shoulders. Physical examination revealed cyanosis, irregular breathing, icterus of skin and sclerae, and an enlarged liver and spleen. The temperature was 101.6° F. on the first day but was normal thereafter. The blood counts were hemoglobin, 135 per cent; erythrocytes, 7,490,000; leucocytes, 18,500; differential: neutrophiles, 78 per cent; lymphocytes, 13 per cent; monocytes, 8 per cent; eosinophiles, 1 per cent; normoblasts, 5 per 100 leucocytes. The icterus index was 129. The van den Bergh reaction was delayed or indirect, indicating obstruction in the liver cells, since there was no blood destruction. The stools were positive for bile. The urine was negative for bile. Three blood cultures taken on the fifth, ninth and nineteenth days were positive for hemolytic *Staphylococcus aureus*. The blood counts on the ninth day were as follows: hemoglobin, 133 per cent; erythrocytes, 7,000,000. The cyanosis and the jaundice gradually disappeared. On the fifty-sixth day the icterus index was 13.5. The diagnosis was infectious jaundice.

At times one sees patients with infectious jaundice who do not recover but develop a cirrhosis. These are difficult to differentiate from jaundice resulting from an anomaly of the bile ducts.

Anomalies of the Bile Ducts.—It is extremely difficult and often impossible clinically or by laboratory findings or surgical exploration to differentiate a jaundice resulting from congenital atresia of the bile ducts from a jaundice of infectious origin.

If the history is sufficiently reliable to convince one that the jaundice appeared after birth, one can be certain that it is not the result of an atresia of the bile ducts. However, it is rare to find a history on a newborn infant that absolutely excludes jaundice at birth. Usually very

little attention is paid to the color of the newborn infant until it is a few days old. Even then the jaundice is often missed unless it is marked. This, no doubt, accounts for the number of cases of jaundice with atresia of the bile ducts reported with jaundice occurring after birth. Other cases reported in which the jaundice appeared from 2 to 4 weeks after birth probably belong in the group with hepatitis or cholangitis.

In some instances the degree of jaundice aids in the differential diagnosis. Ladd[2] believes that jaundice from sepsis does not produce the acholic stools, bile in the urine, a high icterus index, or progressively increasing jaundice that is seen in congenital atresia of the bile ducts. I believe that the higher the icterus index, the less likely is the presence of atresia. If the icterus index is from 200 to 400, it is probably not the result of atresia. Since the jaundice present in an atresia is a regurgitation jaundice, as described by Rich[3] and Watson,[4] bilirubin is being excreted by the kidney, thus preventing the extreme accumulation of bilirubin which occurs in some of the infants with infectious jaundice. However, since a large number of the infants with jaundice resulting from hepatitis or cholangitis have an icterus index as low as from 75 to 150, too often this is not a differential point. The absence of bile pigments in the stools, while compatible with such a diagnosis, is not diagnostic of atresia of the bile ducts. Neither does the presence of a small amount of bile pigment rule out atresia of the bile ducts. A positive blood culture does not always aid in the differential diagnosis, because a patient with atresia of the bile ducts is extremely susceptible to infections and can develop a bacteremia.

In difficult cases in which there is no history or clinical or laboratory findings that aid in the differential diagnosis, only two lines of procedure are available; namely, watchful waiting or exploration. If the jaundice is the result of hepatitis, cholangitis, or cloudy swelling of the liver cells, the infant may show signs of recovery by the eighth to twelfth week. Ladd[2] states that nothing is gained by waiting past the second month, because the diagnosis can be made with great certainty by that time. Rosenberg and Judd[5] reported a case which was diagnosed in an infant 3 weeks of age as congenital atresia of the bile ducts. Surgery was refused by the parents. The jaundice cleared at 3 months. In this case waiting was wise.

Exploration is not always satisfactory. The field is small and if the obstruction is high, as a result of cholangitis or swelling of the liver cells, and there is no filling of the ducts, they are easily missed or, if seen, are described as fibrous cords. Thus an incorrect diagnosis of absence or atresia of the bile ducts is often made. No doubt some recoveries following surgery in these jaundiced infants can be explained on this basis. Donovan[6] reported two cases in infants who are living and well in whom the diagnosis of atresia of the bile ducts was confirmed by exploration.

Autopsy reports on some infants with atresia of the bile ducts are not convincing. Too often it is concluded that an atresia exists because a probe cannot be passed through the ducts which are either normally small or small from disuse. Unless microscopic study shows that the ducts have never recanalized and are not patent, atresia is not established. A descending infection can cause disuse atrophy, scarring, and fibrosis of the ducts. Perhaps this is the type of lesion present in some of the so-called congenital atresias in infants who live twelve or fourteen months. On careful dissection of the bile ducts at autopsy, the ducts are not always found. Unless the hepatico-duodenal ligament with the enclosed ducts and vessels is removed in a block and multiple sections examined microscopically from the ampulla to the liver and gall bladder, there can be no certainty about their absence.

The following cases are presented to illustrate the difficulties encountered in differentiating atresia of the bile ducts and infectious jaundice.

CASE 2.—M. C., a Mexican male, full term, with a birth weight of 7½ pounds, was admitted to the hospital at the age of 1 month because he was anemic. At 2 days of age hemorrhage from the cord had occurred which was controlled by a ligature. Five days later profuse bleeding occurred which was controlled by crushing the stump with a hemostat. Weight on admission was 6 pounds, 7 ounces. Physical examination was negative except for pallor and a systolic murmur. The temperature was normal. The blood counts showed the following: hemoglobin, 42 per cent; erythrocytes, 2,110,000; leucocytes, 10,900. The stools were yellow. Wassermann tests of the mother and patient were negative. Jaundice was not observed. A transfusion of 75 c.c. of whole blood was given. The patient was discharged weighing 6 pounds, 12 ounces. He was followed in the outpatient department; jaundice was not noticed until the age of 2½ months. At 3 months he was readmitted because of increasing jaundice and loss of weight. The mother had noticed that for the past week the stools were light and that the urine was dark and stained the diaper yellow.

Physical examination revealed a malnourished infant with a deep greenish yellow color, with icteric sclerae and a palpable liver.

Examination of the blood showed the following: hemoglobin, 58 per cent; erythrocytes, 3,020,000; leucocytes, 15,450; differential: neutrophiles, 66 per cent; lymphocytes, 30 per cent; eosinophiles, 1 per cent; monocytes, 3 per cent. The icterus index was 95. The van den Bergh test gave a direct reaction. The stools showed a faint trace of bile but were described as clay colored.

At the age of 4 months the infant developed bilateral otitis media. Later a bilateral antrotomy was done, and a culture from the left antrum produced *Streptococcus viridans*. At 5 months of age the patient's weight was 8 pounds, 8 ounces. The liver was three fingerbreadths and the spleen 1½ fingerbreadths below the costal margin. The stools were occasionally reported as yellow; otherwise, they were clay colored. An exploratory laparotomy was done. The liver was described as large; the gall bladder, small and contracted. The cystic, hepatic, and common ducts were small. A probe was passed through the common duct toward the duodenum, but it was not possible to enter the intestine. The conclusion was drawn that an atresia of the common duct existed, although there was no distention of the ducts above. The patient developed bronchopneumonia and expired two weeks after surgery.

Autopsy Findings.—The liver was slightly roughened and of a greenish color; the gall bladder was small and atrophic. The gross description of the biliary system was complete atresia of the hepatic duct and atrophy of the lower portion of the common duct. The duodenum was opened and the ampulla of Vater was clearly visible. Microscopic examination showed diffuse fibrosis of the liver, most intense in the periportal spaces; the hepatic duct was small with thick walls and some destruction of tissue. The lumen was filled with debris composed mostly of lining cells. The gall bladder wall was atrophic. The mucous membrane lining of the gall bladder was edematous and infiltrated with round cells. The cystic duct and the common duct had thickened walls with small lumen but were patent. The history and the microscopic findings could be explained on the basis of an infectious jaundice with a descending inflammatory lesion superimposed on ducts atrophied from disuse.

CASE 3.—R. B., a white male, full term, with a birth weight of 4 pounds, 12 ounces, was admitted to the hospital at the age of 6 weeks with a history of jaundice and acholic stools since birth. Weight on admission was 6 pounds, 12 ounces. Physical examination revealed a markedly icteric but well-developed and well-nourished infant. The liver edge was felt 1 cm. below the costal margin. The tip of the spleen was barely palpable.

The blood counts showed the following: hemoglobin, 80 per cent; erythrocytes, 3,970,000; leucocytes, 13,350; neutrophiles, 65 per cent; lymphocytes, 30 per cent; monocytes, 4 per cent; eosinophiles, 1 per cent. The icterus index was 103. The van den Bergh test gave a direct reaction. The stools were negative for bile. The blood culture was negative.

A diagnosis of congenital atresia of the bile ducts was made, and at the age of 7½ weeks an exploratory laparotomy was performed. A very small gall bladder was found containing a few drops of yellow fluid. A small needle was placed in the gall bladder, but only a small amount of saline could be injected. The gall bladder was dissected from the surface and freed along the cystic duct. The cystic duct apparently joined the common duct. An attempt was made to aspirate bile from what appeared to be the common duct, but only blood was obtained. A probe was inserted into the fundus of the gall bladder and passed down the cystic duct, which seemed to end as a blind sac. Under very slight traction of retaining hemostats, the bladder stalk broke. No anastomosis was attempted. The patient was discharged at the age of 9 weeks with acholic stools and no decrease in the degree of icterus. At 1 year of age he won a prize in a well-baby contest. He is alive and well at the age of 5½ years. This was, without doubt, an infectious jaundice that cleared some time after the ninth week.

CASE 4.—A. T., a 1-month-old infant, was admitted to the hospital with a history of jaundice and acholic stools since birth. An occasional yellow stool was reported. Physical examination revealed a jaundiced infant with an enlarged spleen and liver.

The blood counts showed the following: hemoglobin, 60 per cent; erythrocytes, 3,280,000; leucocytes, 13,950. The icterus index was 136. Prothrombin time was 85 per cent of normal. Two blood cultures produced hemolytic *Staph. aureus*. The Wassermann was negative. Nine examinations of the stools were negative for bile, and one showed a faint trace.

A diagnosis of infectious jaundice was made and verified by a liver biopsy. The biopsy was done under a local anesthesia; the exposure was poor, but it was believed that there was no atresia of the bile ducts. Microscopically the liver showed an increased amount of fibrous connective tissue about the portal structures. In areas

there was proliferation of the small bile ducts and infiltration with small round cells. Some of the liver cells were slightly vacuolated. A diagnosis of chronic cholangitis was made.

The infant returned at the age of 10½ months with an extremely distended abdomen, a cough, a fever of 102.8° F., and edema of the feet. The superficial veins were visible over the upper part of the abdomen, and ascites was present. He expired two days later.

Autopsy Findings.—The liver and gall bladder weighed 260 Gm. The surface of the liver was finely nodular and had a deep green color. The gall bladder was an egg-shaped mass 6.5 by 3.5 by 3.5 cm., from which no normal duct could be traced. The midportion of the gall bladder, however, for a distance of about 2 cm., apparently connected with another cystic mass measuring 2.8 by 3.4 by 1.5 cm. This, in, turn, communicated with several smaller cysts; the entire group made a system of hepatic ducts. No connection between these and the duodenum was made out. No common duct was found. The sections of liver were scarcely recognizable as such. There was enormous proliferation of the periportal connective tissue and proliferation of the small bile ducts. The lobules were small and the liver cells were small and heavily vacuolated. There was considerable pigment deposited throughout the tissue, but the small bile canaliculi were not dilated or filled with pigment. There were areas of slight round cell infiltration of the connective tissue. This was primarily an anomaly of the bile ducts with a superimposed bacteremia and cholangitis.

Erythroblastosis.—In 1932, Diamond, Blackfan, and Baty[7] concluded that universal edema of the fetus, familial icterus gravis neonatorum, erythroblastosis, and anemia of the newborn infant are closely related and that the conception of a certain sequence of events leading to the development of each symptom complex is justified.

In 1940, Landsteiner and Wiener[8] discovered the Rh factor in the red cells. Landsteiner and Wiener[9] and Levine[10] found that 85 or 86 per cent of the population are Rh positive, and 14 per cent or 15 per cent are Rh negative. However, Levine, Vogel, Katzin, and Burnham[11] and Levine, Burnham, Katzin, and Vogel[12] have shown that 90 per cent of the mothers who give birth to infants with the above syndrome are Rh negative. This percentage is too high to permit any doubt that it is at least part of a certain sequence of events leading to the development of this syndrome. At present, the general belief is that it is the sole cause.

The theory presented is that the Rh-positive cells of the fetus enter the mother's blood stream and build up an anti-Rh factor in the mother's plasma. This anti-Rh factor in turn enters the fetal circulation and hemolyzes the erythrocytes of the fetus. On analysis, only the extreme cases, namely, the universal edema of the fetus, might be explained solely on this theory. Since these infants are usually born dead and macerated, they do not supply much material for scientific study. The milder cases—anemia of the newborn infant, erythroblastosis, icterus gravis—are in living infants and upon study present findings that are difficult to explain on the Rh factor alone.

The onset of the jaundice in many instances is after birth. Although some of these infants are born anemic and jaundiced, the majority of

them are born with a high erythrocyte count and no jaundice. The anemia and jaundice appear from twenty-four to forty-eight hours after birth. If the anemia resulted from hemolysis of the red cells by the anti-Rh factor from the mother's plasma, one would expect this phenomenon to be most marked before birth instead of from twenty-four to forty-eight hours later. Furthermore, there is never any hemolysis of the erythrocytes. Hemoglobinemia and hemoglobinuria are never found in this group. Instead, a hyperactivity of the reticulo-endothelial system occurs, resulting in phagocytosis of the erythrocytes. In all other reactions of the anti-Rh factor on the Rh-positive cells, there is true hemolysis.

One might argue that it is the anti-Rh factor which stimulates the reticulo-endothelial cells to produce the severe degree of anemia, even though it failed to do so before birth. If one granted that this were true, there still is no explanation why the addition of Rh-negative cells by transfusion fails to maintain the erythrocyte level. These Rh-negative cells are destroyed within a few days or hours. Rh-positive cells are destroyed at the same rate, but still without the hemolysis which occurs in other transfusions of Rh-positive cells to a patient with the anti-Rh factor. Also, one or two transfusions of Rh-positive blood should neutralize the anti-Rh factor present and permit the erythrocyte level to rise. Instead, there is a continuation of the blood destruction for weeks and in some cases, for from two to four months. Consequently the persistent anemia and blood destruction cannot be explained without considering some new etiologic factor having made its appearance during birth or shortly after birth.

The degree of jaundice seen in these patients cannot be explained on blood destruction alone. The icterus index ranges from 75 to 600. Such a degree of jaundice indicates liver involvement. Hepatitis, cholangitis, or cloudy swelling evidently do not occur before birth in the infants who are not jaundiced at birth. Why should the anti-Rh factor become such a toxic agent after birth?

Ten per cent of the infants with erythroblastosis are born of Rh-positive mothers. The father and infant are also Rh positive. These infants have the same symptom complex and run the same course. Do they have the same disease even though the anti-Rh factor is not an etiologic agent?

The blood picture is not diagnostic of this group. Congenital syphilis, sepsis, and familial jaundice may produce a similar blood picture with many erythroblasts. The significant findings in the blood picture are the leucocytosis and the changes seen in the leucocytes. There is a neutrophilia and a monocytosis which persist for months. The immaturity in the monocytes and the presence of reticulo-endothelial cells often persist after the immaturity in the other cell lines disappears. This immaturity in the monocytes, which goes back to the reticulo-endothelial cell, is the same as is seen in bacteremias and in cases de-

scribed as infectious reticulo-endotheliosis. At times I have seen numerous bacteria engulfed in the reticulo-endothelial cells in some of these cases.

Dunham[13] and others have reported cases of sepsis of the newborn with positive blood cultures. Some of these have had sufficient findings to place them in the erythroblastosis group. However, it is usually customary to call these sepsis of the newborn when the blood cultures are positive; when the cultures are negative, they are called erythroblastosis.

The placental changes that have been described are edema, multiple intraplacental hemorrhages, thickening of the villi, and periarteritis of the fetal vessels. This damage to the placenta is no doubt one of the sequence of events leading to erythroblastosis. It sets the stage for what is to follow. Is it possible that in the infants with erythroblastosis and icterus gravis who are not born jaundiced and anemic that this injured placenta permits the entrance of bacteria during birth? If so, in multipara who have had one or more babies with erythroblastosis or icterus gravis, could we prevent further occurrence by cesarean section two or three weeks before term?

FAMILIAL JAUNDICE

Since familial jaundice may be present at birth, it is necessary to consider such a diagnosis in any jaundiced and anemic newborn infant. A familial history is not always obtainable; nevertheless, upon examination of the members of the family, evidence of this disease usually can be found. The usual names applied to this disease are congenital hemolytic jaundice, familial hemolytic jaundice, chronic hereditary hemolytic jaundice, and chronic acholuric jaundice. It is hereditary, familial, and often congenital, but it is never hemolytic. Hemoglobinemia and hemoglobinuria are never present in this disease.

The diagnosis of familial jaundice is not difficult. The one reliable diagnostic point is the blood picture. Although there may or may not be marked anisocytosis, polychromasia, basophilic stippling, and a number of normoblasts, there is always a number of microcytes which are spherical and take the stain deeply. These microcytes appear to be overfilled with hemoglobin and are conspicuous in the midst of the larger red cells which contain a normal or decreased amount of hemoglobin.

The fragility test is diagnostic if the red cells hemolyze in 0.50 per cent sodium chloride solution or above, provided the control is not above 0.44 per cent. If the fragility of the red cells is not increased, it does not rule out familial jaundice. However, in familial jaundice, if the fragility test is repeated over a period of time, an increased fragility will be found eventually. False conclusions are often drawn from a single negative result.

The findings of interest in familial jaundice are the anemia, reticulocytosis, jaundice, splenomegaly, hepatomegaly, enlarged heart, rarefac-

tion of the bones, and delayed ossification centers. These vary markedly, and it is on these variations that familial jaundice is classified as mild, moderate, or severe.

The mild cases are rarely seen in infancy or early childhood. Unless an acute infection brings on a crisis, children so affected may not become jaundiced before adulthood or they may go through life undiagnosed. Those cases of jaundice which appear for the first time in middle life are often considered acquired jaundice. In these patients with mild cases anemia and increased regeneration are present only following an attack. The spleen may not be palpable. Splenectomy produces a complete cure.

One might question whether splenectomy is indicated in these patients with mild cases. Since there is always the danger of an acute infection producing an uncontrollable crisis, splenectomy is justifiable. This point is illustrated in Case 6.

CASE 5.—L. B., a white female, aged 2½ years, was admitted to the hospital because of anemia and jaundice. For one week before admission she had had an upper respiratory infection, fever and diarrhea, and became jaundiced for the first time. On physical examination the liver was felt one fingerbreadth below the costal margin; the spleen was not palpable.

The blood counts were as follows: hemoglobin, 30 per cent; erythrocytes, 1,610,000; leucocytes, 20,200. Reticulocytes were 13.4 per cent. The blood smear showed dark spherical microcytes. Hemolysis of the patient's red cells began in 0.48 per cent sodium chloride solution and was complete in 0.30 per cent. The control began in 0.42 per cent and was complete in 0.32 per cent. The icterus index was 56.

Three transfusions were given and the infection was treated with sulfathiazole. Two weeks later the blood counts were as follows: hemoglobin, 66 per cent; erythrocytes, 3,860,000; leucocytes, 10,500. The reticulocytes were 3.2 per cent. Nine months later the patient had had no recurrence of the anemia or jaundice. Splenectomy has not been done.

CASE 6.—L. M., a white female, aged 10½ years, was well until four months before admission to the hospital. She had had an upper respiratory infection with a cough but no fever. The cough persisted for three weeks. Six weeks before admission she had pain, redness, swelling, and tenderness in her joints, moving from one joint to another. Three weeks later she began to have chest pain, which was accentuated by respirations.

Physical examination revealed a heart that was enlarged to the right and to the left; there was a loud systolic murmur, loudest at the base. The spleen was enlarged to percussion; the liver was palpable two fingerbreadths below the costal margin.

The blood counts were as follows: hemoglobin, 38 per cent; erythrocytes, 1,900,000; reticulocytes, 42 per cent. The blood smear showed dark spherical microcytes. Hemolysis of the red cells began above 0.50 per cent sodium chloride solution and was complete in 0.36 per cent. In the control, hemolysis began in 0.44 per cent and was complete in 0.30 per cent. The icterus index was 19 on admission and rose to 43 later.

The child ran a febrile course for two months and did not improve sufficiently to permit splenectomy. After seven blood transfusions the blood counts were as follows: hemoglobin, 12 per cent; erythrocytes, 710,000; leucocytes 39,600. There

were 10 normoblasts per 100 leucocytes. The reticulocytes were 24.4 per cent. The significant autopsy findings were pleurisy, pericarditis, and myocarditis with abscesses.

The moderate cases are the most frequent in infancy and childhood. The patients have several attacks of jaundice in early life. The hemoglobin and erythrocyte levels may return to normal during remissions or a mild degree of anemia with a moderate reticulocytosis may persist, indicating a mild constant blood destruction. The color index is 1 or slightly below 1. The fragility of the erythrocytes is not always increased. The spleen is usually palpable; the liver may become enlarged if the blood destruction is constant. The icterus index may return to normal during remissions; however, if there is a constant mild anemia from blood destruction, there will be a subclinical icterus.

The constant anemia in infancy or early childhood produces an enlarged globular heart and delayed ossification centers. If the blood destruction and regeneration is constant in infancy, rarefaction of the bones occurs.

It is extremely important that these cases are diagnosed early and that splenectomy is done in early childhood. If splenectomy is done too late, a complete recovery may not occur. The blood destruction, the anemia, and jaundice may persist and the bone changes may progress. Therefore, if a mild degree of anemia persists and there is a slight enlargement of the heart, beginning rarefaction of the bones, or the presence of delayed ossification centers, early splenectomy is indicated.

CASE 7.*—W. B., a full-term infant with a birth weight of 8 pounds, was born with no anemia and no jaundice. His mother had a splenectomy at the age of 17 years for familial jaundice. Her anemia had been constant and she had skull changes. Her recovery was not complete. She still has a subclinical icterus and, at times, a mild clinical icterus. Her father had a splenectomy at the age of 44 years and her sister, at the age of 19 years, with complete recovery. The patient's sister had familial jaundice.

The infant's blood counts at 2 months of age showed the following: hemoglobin, 55 per cent; erythrocytes, 3,080,000; leucocytes, 7,150; reticulocytes, 11 per cent. The blood smear showed increased regeneration with an occasional dark spherical microcyte. The icterus index was 12. Hemolysis of the red cells began in 0.44 per cent sodium chloride solution and was complete in 0.32 per cent. The control began in 0.42 per cent and was complete in 0.32 per cent. At 6 months of age the spleen was palpable 1 cm. below the costal margin. At no other time was it palpable. At 18 months of age a mild upper respiratory infection produced a clinical jaundice and a hemoglobin level of 45 per cent. Otherwise, during two and one-half years his blood levels were as follows: hemoglobin, from 60 to 70 per cent; erythrocytes, 3,000,000 to 4,500,000; reticulocytes, 4.5 to 11 per cent. The icterus index ranged from 12 to 20. The fragility test was not abnormal. At two and one-half years of age roentgenograms showed slight changes in the skull and long bones as a result of the constant increased regeneration in the red cells. Splenectomy was performed,

*Courtesy of Dr. Hugh Berkley.

and the recovery was complete. A fragility test after splenectomy showed hemolysis of the red cells beginning above 0.50 per cent sodium chloride solution and was complete in 0.34 per cent. The control began in 0.38 per cent.

The severe cases usually present themselves at birth or in early infancy. These may be diagnosed erythroblastosis. The anemia, the blood destruction, and a marked reticulocytosis are continuously present. As a result of the constant blood destruction followed by marked regeneration, a definite sequence of events follows. They maintain an increased amount of bilirubin in the blood, so that they always have a clinical or subclinical icterus. The heart becomes large and globular. The liver and spleen become enlarged. Rarefaction of the bones results from the hyperplastic marrow. The anemia becomes macrocytic as well as microcytic. The macrocytes are pale and have the hemoglobin arranged in a ring around the periphery of the cell (anochromasia). There is marked polychromasia, erythroblasts, and a high reticulocyte count. Such a condition is apt to be called Cooley's anemia, if it occurs in the Mediterranean races.

Since these changes occur in infancy, it is important that an early diagnosis is made and that splenectomy is performed as early as possible. If splenectomy is delayed, complete recovery does not occur. Occasionally a case is so severe that complete cessation of symptoms does not occur with splenectomy done as early as at 2 months of age (Case 9).

CASE 8.—D. P., a Mexican female, had a brother with familial jaundice and two brothers and one sister who died at birth. She became jaundiced at the age of 2 months. At 4 months of age her blood counts showed the following: hemoglobin, 43 per cent; erythrocytes, 2,230,000; leucocytes, 15,360. The blood smear showed dark spherical microcytes. The icterus index was 15. Hemolysis of the red cells began above 0.50 per cent sodium chloride solution and was complete in 0.38 per cent. The control began in 0.44 per cent and was complete in 0.34 per cent. The patient was given a transfusion and followed in the outpatient department. She was constantly anemic; at 8 months of age she was given another transfusion. At 16 months of age she developed an upper respiratory infection and bilateral otitis media. Her blood counts were as follows: hemoglobin, 27 per cent; erythrocytes, 2,090,000. Icterus index was 17. Roentgenograms showed slight bone changes. At 22 months of age she was admitted for splenectomy. The spleen and liver were both palpated two fingerbreadths below the costal margin. The blood counts were as follows: hemoglobin, 35 per cent; erythrocytes, 2,540,000. The icterus index was 27. The anemia had been constant and severe, the bone changes had progressed, the ossification centers were delayed in development, and the heart was globular, yet her recovery was complete.

CASE 9.—C. R., a white female, was a full-term infant, weighing 6 pounds, 4 ounces. There was a history of jaundice in the maternal grandmother. Jaundice and anemia were first noticed in this infant at the age of 12 days. A tentative diagnosis of erythroblastosis was made. The blood counts showed the following: hemoglobin, 28 per cent; erythrocytes, 2,110,000; leucocytes, 45,050. There were 10 normoblasts per 100 leucocytes. The blood smear showed numerous dark spherical microcytes and marked fragmentation of the red cells. Four transfusions were given at another hospital between the ages of 12 days and 2 months. At the age of 2

months, the patient was admitted to the Children's Hospital for splenectomy. The blood counts were as follows: Hemoglobin, 30 per cent; erythrocytes, 1,820,000; leucocytes, 14,670. There were 10 normoblasts per 100 leucocytes. The spleen weighed 120 Gm. (normal, 13 Gm.). Although the patient had received 100 c.c. of whole blood, the blood counts sixteen days after splenectomy were as follows: hemoglobin, 52 per cent; erythrocytes, 3,580,000. Two years later the blood counts were as follows: hemoglobin, 67 per cent; erythrocytes, 4,820,000; leucocytes, 16,800; reticulocytes, 12.4 per cent. Roentgenograms showed slight bone changes. Three and one-half years after splenectomy the blood counts were as follows: hemoglobin, 75 per cent; erythrocytes, 5,540,000; leucocytes, 17,800; reticulocytes, 14.8 per cent. The blood smear showed many spherical microcytes, increased regeneration, and marked fragmentation of the erythrocytes (Fig. 1). The roentgenograms of the skull and long bones showed progression of the bone changes. Recovery has not been complete.

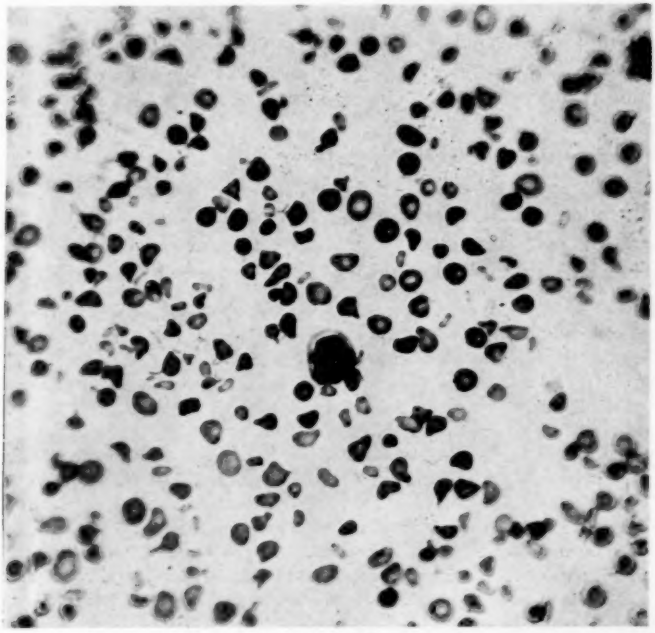

Fig. 1 (Case 9).—C. R. Blood smear three and one-half years after splenectomy showing dark spherical microcytes and marked fragmentation of the erythrocytes.

CASE 10.—F. H., a white male, was anemic early in infancy. At 3½ months of age his blood counts were as follows: hemoglobin, 45 per cent; erythrocytes, 2,730,000; leucocytes, 13,150. Hemolysis of the red cells began in 0.48 per cent sodium chloride solution and was complete in 0.38 per cent. The control began in 0.46 per cent and was complete in 0.36 per cent. The diagnosis was secondary anemia, although a diagnosis of familial jaundice must have been considered, since splenectomy was advised four months later. He did not return to the clinic until he was 9 years of age. At this time he was crying with pain in the upper left quadrant. The skin and sclerae were yellow and his features suggested a mongoloid appearance. The spleen was enlarged to the level of the umbilicus. The blood counts

were as follows: hemoglobin, 51 per cent; erythrocytes, 2,980,000; leucocytes, 16,900. There were 2 normoblasts per 100 leucocytes. The reticulocytes were 71 per cent. The blood smear showed dark spherical microcytes. The icterus index was 36. Hemolysis of the red cells began above 0.50 per cent sodium chloride solution and was complete at 0.28 per cent. The control began at 0.42 per cent and was complete at 0.32 per cent. Roentgenograms showed changes characteristic of anemia in the skull, long bones, and bones of the hands. The heart was large and globular.

Fig. 2 (Case 11).—B. H. Bone changes in skull before splenectomy.

Splenectomy was performed. The spleen weighed 462 Gm. (normal, 72 Gm.), and the lower pole had an infarct with cystic degeneration. Twenty-two days after surgery the blood counts showed the following: hemoglobin, 55 per cent; erythrocytes, 2,890,000; leucocytes, 17,550; reticulocytes, 68.4 per cent.

Three months after splenectomy cyanosis was noticed. The reticulocytes were 100 per cent. Cyanosis, anemia, and variable degrees of icterus persisted. Transfusions, which lower the reticulocyte count, decreased the cyanosis. At 15 years of age he had an acute attack of pain in the upper right quadrant. Gallstones were demonstrated in a flat plate of the abdomen. Seven years after splenectomy his

blood counts are as follows: hemoglobin, 57 per cent; erythrocytes, 2,890,000; leucocytes, 22,200. The reticulocytes are 100 per cent. The blood smear shows marked regeneration and marked basophilic stippling. There has been no improvement following splenectomy.

Fig. 3 (Case 11).—B. H. Bone changes in skull nearly three years after splenectomy.

CASE 11.*—B. H., a white female, aged 14 years, had had attacks of jaundice since birth. No record was obtainable of any previous blood counts. She had had pyelitis, measles, mumps, and chicken pox. Her condition had not been diagnosed as familial jaundice until the day before admission to the hospital. Physical examination revealed a well-developed female with a clinical icterus. The spleen extended one fingerbreadth below the level of the umbilicus. The liver edge was palpable. Roentgenograms showed marked thickening of the skull (Fig. 2).

The blood counts were as follows: hemoglobin, 55 per cent; erythrocytes, 2,800,000; leucocytes, 10,750. The blood smear showed dark spherical microcytes.

*Courtesy of Dr. Louis Martin.

The icterus index was 40.5. Hemolysis of the red cells began in 0.44 per cent sodium chloride solution and was complete in 0.18 per cent. The control began in 0.44 per cent and was complete in 0.28 per cent. A spleen weighing 492 Gm. and an accessory spleen were removed; 450 c.c. of citrated blood were given following surgery. Sixteen days later the blood counts were as follows: hemoglobin, 55 per cent; erythrocytes, 2,830,000; leucocytes, 14,000; reticulocytes, 6.6 per cent. The icterus index was 19. Nine months later cholecystectomy was performed because of numerous gallstones. At this time the blood counts were as follows: hemoglobin, 53 per cent; erythrocytes, 2,910,000; leucocytes, 15,680; reticulocytes, 27.4 per cent; 16 normoblasts per 100 leucocytes. Nearly three years after splenectomy the blood counts were as follows: hemoglobin, 41 per cent; erythrocytes, 2,480,000; leucocytes, 22,600 (corrected for normoblasts); reticulocytes, 36.8 per cent; 183 normoblasts per 100 leucocytes. Roentgenograms of the skull showed progression of the bone changes (Fig. 3). There was no improvement following splenectomy.

Consideration of the variable degrees of familial jaundice throws some light on the reports of the value of splenectomy in this disease. McLaughlin and Sharp[14] were, no doubt, dealing with only the mild cases when they claimed that splenectomy always produces permanent relief of symptoms and that failure to do so proves an incorrect diagnosis. Haden[15] also was considering the mild cases when he stated that splenectomy always cures the symptoms of the disease.

It is necessary to classify familial jaundice as mild, moderate, or severe in order to advise treatment. Patients with mild cases have permanent relief of symptoms whenever splenectomy is done. Those with moderate cases should have splenectomy performed early in childhood; in the severe cases splenectomy is necessary in infancy, if recovery is to be complete.

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Proceedings

The Executive Board of the American Academy of Pediatrics met at the Palmer House, Chicago, at 10 A.M., Nov. 6, 1943, with Dr. Borden S. Veeder in the chair.

The following applicants were approved:

Region I

Dr. Frank Herbert Boone, 137 Mountain Park Ave., Hamilton, Ont., Can.
Dr. J. Frederick Close, 66 Milbank Ave., Greenwich, Conn.
Dr. Harold L. Davis, 178 W. State St., Trenton, N. J.
Dr. Joyce Victoria Deutsch, Southbury Training School, Southbury, Conn.
Dr. Samuel Dillon, 119-02 Blvd., Rockaway Park, N. Y.
Dr. John Robert Gilmour, 144 South Harrison St., East Orange, N. J.
Dr. Mildred G. Gregory, 64 North Ninth St., Newark, N. J.
Dr. Alexander D. Gross, 9034 214th St., Queens Village, L. I., N. Y.
Dr. Abram Kanof, 80 Linden Blvd., Brooklyn, N. Y.
Dr. William O. Kopel, 907 Crawford Ave., Syracuse, N. Y.
Dr. Joseph H. Lapin, 1166 Grand Concourse, Bronx, N. Y.
Dr. Albert Upham Peacock, Hartford, Conn. (In service.)
Dr. Ellsmer Landis Piper, Medical Arts Bldg., 3710 Fifth Ave., Pittsburgh, Pa.
Dr. Oscar McClellan Race, 100 Central Ave., Staten Island (1), N. Y.
Dr. Benjamin Stein, 1835 Eye St., N.W., Washington, D. C.

Region II

Dr. Donald F. Cathcart, 478 Peachtree St., Atlanta, Ga.
Dr. Eleanor Cook, Lake Charles, La.
Dr. C. Hall Farmer, 118 Pio Nona Ave., Macon, Ga.
Dr. Claude C. McLean, 2012 Tenth Ave., South, Birmingham, Ala.
Dr. Robert L. Moore, 3403 Hall Street, Dallas, Texas.
Dr. Ralph Victor Platou, 1430 Tulane Ave., New Orleans, La.
Dr. J. Sam Smith, 4 Catoma St., Montgomery, Ala.
Dr. Cecil Stuart E. Touzel, 1324 Summit Ave., Fort Worth, Texas.

Region III

Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee (2), Wis.
Dr. Ruben Meyer, 938 Maccabees Bldg., Detroit, Mich.
Dr. Herman B. Lander, 613th Bomb. Squadron (H), AAB, Cut Bank, Mont.

Region IV

Dr. Donald L. Gillespie, Murry Clinic, Butte, Mont.
Dr. Edward A. Hagmann, 1128 N. 32nd St., Billings, Mont.
Dr. Margaret H. Jones, State Board of Health, State Capitol, Cheyenne, Wyo.
Dr. Orlindo Louis Ross, 1015 Boston Bldg., Salt Lake City, Utah.

Dr. Harry R. Carson, Phoenix, Ariz., Dr. Stanley D. Giffen, Toledo, Ohio, and Dr. James K. Everhart, Pittsburgh, Pa., were transferred from Active to Emeritus Fellowship.

Dr. Lee Frech, Decatur, Ill., was reinstated. The resignation of Dr. Annie S. Veech, Louisville, Ky., was accepted.

In the report of Region I, Dr. Nichols, who is serving his last term as chairman, detailed the activities of the region in the various states. He expressed his inter-

est in the conditions of the child following the war and detailed the measures which he felt would be of value. (Report appended.)

Dr. Moore, for Region II, stated that he was endeavoring to obtain a vote of his region for redistricting the Academy into three districts.

Dr. Lee Forrest Hill, for Region III, recorded the request of the Nebraska Pediatric Society for national regional meetings; also, the remarks of several other state groups on this proposition. (Report appended.)

Dr. Hugh K. Berkley of Region IV had nothing special to report.

For Region V Dr. Clifford G. Grulee reported that there were now ninety-nine members and presented the names of the following who were elected to membership:

Dr. Dalmacio Azevedo
Dr. Raul Moreira
Dr. Leite Bastos
Dr. Carlos Hofmeister
Dr. Osanah de Oliveira
Dr. Mario Esberard Leite
Dr. Marcelo Garcia
Dr. Eduardo Imbassahy
Dr. Melo Teixeira

Likewise, Dr. Dante Costa of Brazil was elected an associate member.

At the suggestion of Dr. Felix Hurtado of Cuba, the Executive Board discussed the representation on the board of members of Region V and other matters looking to a closer cooperation of Region V with the Academy. The suggestions contained in Dr. Hurtado's letter had a cordial reception from the Board and it was suggested, in order to further these ideas, that the secretary be asked to obtain from the various members in Latin-American countries their ideas as to how this could best be brought about.

In connection with this, the secretary reported on the Pan-American scholarships, showing that there were fourteen Pan-American scholars at present in this country and that there were nineteen scholarships. S. M. A. Corporation has recently given a scholarship of $1,500 a year for three years. Mead Johnson & Company has renewed its scholarship for the same period, while the one given by the Abbott Laboratories has been discontinued. There are a total of twenty-three clinics in the United States and Canada where such scholars could be received. It has been arranged for scholars in this country to translate the abstracts which are being sent to the members in Latin-American countries, which is a great help.

Reports of Committees

Committee on National Defense

Dr. Philip M. Stimson, chairman, reports as follows:

1. Refugee children have continued to come in in small numbers under the auspices of the United States Committee for the Care of European Children. Dr. Carl H. Smith has supervised their medical care during their so-called quarantine period and has done an excellent job.

2. I have been elected to the Board of Directors of the United States Committee for the Care of European Children, presumably to represent the Academy of Pediatrics thereon.

3. I have written the president, asking him to accept my resignation as chairman of the Committee on National Defense. I have not been well, and I shall have to curtail as many activities as possible for this coming winter. I hope I may be allowed to continue as a member of the Committee, because I am interested in its work.

Committee on School Health

Dr. Harold H. Mitchell, chairman, reports as follows:

I have no report of the Committee on School Health except that we are still trying to get the report of last November to the attention of educators. It was presented at the National Conference for Cooperation in Health Education and, at my suggestion, a committee is being appointed in that group to meet with three representatives of our American Academy of Pediatrics Committee to consider the whole matter with a view to preparing a statement that educators will accept as their own and so give it publicity. Dr. Derryberry, Chief of Field Activities in Health Education of the United States Public Health Service, is chairman of the National Conference, and he has asked my advice regarding the composition of this committee. As he is a consultant for the United States Office of Education, I expect he may be able to negotiate with the United States Office of Education so that they may give a widespread distribution of the report.

The Committee on Professional Education of the American Public Health Association has a subcommittee on the qualifications of school physicians which will present a report this week that is entirely consistent with the American Academy of Pediatrics report. Two members of the American Academy of Pediatrics Committee were represented on this American Public Health Association Committee.

Dr. Wheatley of the American Academy of Pediatrics Committee has prepared a chapter on Trends in School Health for the *Review of Educational Research*. This was prepared at the request of the chairman of the board of the American Educational Research Association, J. Cayce Morrison.

A section on school health has been organized in the American Public Health Association. The point of view carried by the Committee on School Health of the American Academy of Pediatrics will probably prevail in this new branch of the American Public Health Association. Dr. Wheatley is secretary of this new section and I am vice-chairman.

Committee on Pan-American Scholarships

Dr. Henry F. Helmholz, chairman, reports as follows:

Since our last report the Committee on Pan-American Scholarships has acted in an advisory capacity to Dr. Grulee, who has taken over the work of the committee. The amount of work that had to be done when the committee was taking care of three or four scholarships, as was the case at the beginning, made us realize that with twenty scholarships it would take pretty nearly half the time of one individual to look after this properly.

We can report that the S. M. A. Corporation has very generously granted the American Academy of Pediatrics a Latin-American scholarship.

Committee on Medical Education

Dr. Joseph A. Johnston, chairman, reports as follows:

Plans are under way to provide for refresher courses in pediatrics for men returning from service, canvasses being made of available facilities. More detailed announcements will appear later.

Committee on Legislation

Dr. Joseph S. Wall, chairman, reports as follows:

Since the last report of the Committee on Legislation, the Act of Congress providing funds for the care of service men's wives and children, to be distributed under the auspices of the Children's Bureau, was passed, and recently additional funds amounting to $18,600,000 were added to the original appropriation of $4,400,000 by a deficiency appropriation which, however, restricted the expenditure of these funds to the care of wives and infants of soldiers in the four lowest grades of enlisted men.

Between July 1 and October 1, wives and infants of service men in the top three grades below commissioned officers were also covered. These are now barred.

The aid of the state chairmen was invoked (being wholeheartedly granted) to defeat an objectionable "rider" inserted in the bill through the machinations of cultists, especially osteopaths, which contained the proviso: "Provided, that no part of any appropriation contained in this title shall be used to promulgate or carry out any instruction, order, or regulation relating to the care of obstetrical cases which discriminates between persons licensed under State law to practice obstetrics. . . ."

The Congress did not include in the restrictions noted the infants or crippled children of the members of the Armed Forces to whom may still be extended skilled services as measured by proper qualifications set forth by administrative authorities.

All but four states have had plans approved for participation in the Federal appropriations. Although certain differences of professional opinion among the residents of the states have developed concerning the administration of the funds, which remain under discussion, it seems probable that these difficulties will be ironed out through further conferences among those concerned with administering and carrying out the program and that equitable solutions may be secured based largely upon the results of experience.

Committee on Rheumatic Fever

Dr. Alexander T. Martin, chairman, reports as follows:

Members of this committee attended a national conference on rheumatic fever and heart disease held in Washington, D. C., on Oct. 5 to 7, 1943, under the auspices of the Children's Bureau. The purpose of this conference was to hear reports from the states conducting services for care of children with rheumatic fever under the Social Security Act, Title V, Part 2; to discuss with many groups and national organizations the overall problem of rheumatic fever in the civilian population and the Armed Services; and to consider a proposal to establish a national foundation for the study of this disease. It is obvious from this conference that interest in the care of rheumatic children is increasing; that in one way or another active programs for their care are well under way; and that many groups are concentrating their efforts in a coordinated movement to control this disease.

It is pointed out to members of the Academy that an important impetus to this movement came from a resolution adopted at a meeting of Region I of the Academy in Rochester, N. Y., in 1938, requesting the Children's Bureau to include rheumatic children in the category of crippled children entitled to aid under the Social Security Act, Title V, Part 2. For this reason and for others based on the inherent responsibility of the Academy as a national organization, as a state group where Children's Bureau programs are in force, or are contemplated, and as individual members in the problem, your committee recommends that the Academy accept this responsibility and continue its interest in and aid to the Children's Bureau program; that the Academy assist in the organization of a national foundation to direct activities in this field; and that the Academy formulate a program of its own.

No other matters have come before the committee.

It is recommended that the committee continue its activities and that it be made permanent.

A more extensive report of the committee is being mimeographed and sent to all members of the Academy.

The following report from the **American Board of Pediatrics** was presented by Dr. Hugh McCulloch and Dr. A. A. Walker, representatives on the American Board of Pediatrics.

The members of the American Board of Pediatrics appointed by the American Academy of Pediatrics submit the following report of the work of this Board from Oct. 1, 1942, to Oct. 1, 1943:

As in the past, we are holding both written and oral examinations for all eligible candidates. Four examinations have been held since the last report as follows: Chicago, Ill., Nov. 2 and 3, 1942; New York, N. Y., Dec. 4, 5, and 6, 1942; St. Louis, Mo., March 27 and 28, 1943; and New York, N. Y., April 23 and 24, 1943.

In these four examinations held during this period, 283 candidates were examined, just ten more than during the similar period last year. Of this group, 71 per cent passed and were certified, while 29 per cent either failed or were conditioned in one subject. As you will note, the mortality is 7.4 per cent higher than last year. We might add that the last two examinations showed a decided rise in the mortality rate, the rates being 38 per cent and 34 per cent, respectively. As far as we can tell there seems to be two reasons for this increase in mortality; first, the applicants who are now in the service, away from the specialty, seem to be letting themselves slip very much, either from lack of time or lack of opportunity to keep up in pediatrics. The second group is the group of older applicants coming up under the ten-year rule that are just barely getting under the line and are poorly prepared and poorly educated.

As you undoubtedly know, the Directory of Medical Specialists was not published this year, but we are continuing to support both the Directory and the Advisory Board for Medical Specialties. The War Department and the Advisory Board for Medical Specialties have abolished the Central File inasmuch as it had served its purpose in so far as the Armed Forces are concerned. To date we have had only one complaint from a licentiate in the Armed Services regarding treatment. Many of our licentiates are not in pediatric or allied branches, but I believe the War Department is doing the best that can be done.

To date, we have not made any change in our ruling regarding applicants being called into service or already in service. This is to be discussed thoroughly at the annual meeting on November 19, 1943. The application fee remains at $50, and there seems to be no indication that this will need to be raised for some time to come.

There has been considerable change in the personnel of the Board since the last report. Due to the death of our president, Dr. Horton Casparis, in November, 1942, shortly following our annual meeting last year, Dr. E. B. Shaw became acting president automatically since he was the vice-president. Dr. M. Hines Roberts of Atlanta, Ga., was elected by the Section on Pediatrics of the American Medical Association to fill Dr. Casparis' unexpired term of six years. Dr. C. A. Aldrich was re-elected by the American Pediatric Society for a term of six years and all other members of the Board remain the same. Dr. Harold Stuart, one of the members elected by your organization, is still interned with the Diplomatic Staff of the United States at Baden Baden, Germany, according to the last report.

During the next nine months the following oral examinations will be held: New York City, Nov. 20, and 21, 1943; Cincinnati, Dec. 10 and 11, 1943; Philadelphia, March 25 and 26, 1944; and San Francisco, May 6 and 7, 1944. All applicants for fall examination will take their written examinations on Oct. 8, 1943, while all applicants for spring examination will take their written on Feb. 4, 1944.

The **Nominating Committee** nominated for President, Dr. Joseph S. Wall, and for Chairman of Region I, Dr. Oliver L. Stringfield. It should be stated that Dr. Alexander T. Martin was unable to accept the chairmanship of Region I, and the Nominating Committee persuaded Dr. Stringfield to accept this position. Report accepted and Drs. Wall and Stringfield declared elected.

The **Treasurer's report** was accepted. (Copy appended.)

The resignation of Dr. Ernest Caulfield was accepted with regret and the appointment of his successor was left to a committee to be appointed by the president.

E. Mead Johnson Awards were voted as follows on recommendation of the committee, of which Dr. Harold Faber was chairman: First, Dr. Hattie E. Alexander, New York, N. Y., and second, Dr. Philip Levine, Newark, N. J.

After discussion of proposed rationing of milk for babies, the following resolutions were adopted:

> The Executive Board of the American Academy of Pediatrics, an organization of some 1,600 pediatricians, views with apprehension the effects upon the child population of the United States through the shortage of fluid milk, and should such shortage prove serious, the possible adoption of inappropriate and inequitable rationing which would not safeguard the interests of infants and young children.
>
> The Executive Board, on behalf of the organization it represents and for which it is authorized to act, would strongly urge that any system of rationing in contemplation or later adopted will make specific provision that each infant and child be assured a ration of fluid milk, or its equivalent, of not less than one quart per day under the age of 2 years, nor below one and one-half pints per day from the age of 2 to 18 years, in order to insure the health of the young, this quantity, in the opinion of pediatricians, being a basic requirement for adequate nutrition.
>
> In addition, the Executive Board would urge that the distributors of fluid milk under the present quota system be authorized to allot at least one quart per day to infants born subsequent to June, 1943, to pregnant and nursing mothers, and to other children changing over from maternal or other form of milk feeding, subsequent to the restrictive date named above, without the complicated system of appeal order by the War Food Administration in F.D.O. 79—#1401; 29, 12, (b), 2, ii and 4, (g), under the heading "Relief from hardship," relating to certification through the "market agent" to the Director of Food Distribution who is vested with final authority to approve such appeal.

At the suggestion of Dr. Joseph S. Wall, who investigated the situation, it was also voted to send the following resolutions to the O.P.A. regarding children's shoes:

"The Executive Board of the American Academy of Pediatrics, an organization of children's specialists throughout the United States, would strongly urge a more liberal production and allocation of children's shoes and would point out that present rulings fail to take into account excessive wear and growth requirements which, obviously, are in no way comparable to adult usage.

"The Executive Board would suggest and ask that a value of four pairs of shoes per year be permitted for children under the age of 10 years, in place of the present 2, in order to protect the health of the young."

The question of letterheads was discussed and changes were agreed upon. It was decided that the Directory should appear as an alphabetical list and a geographical list as states under United States, Canada, and Latin-American countries.

The difficulties regarding framing of certificates was discussed, and the matter was left in the hands of the secretary.

After discussion of the question of postgraduate courses in pediatrics after the war for members of the Academy, it was decided that the matter was being amply taken care of by the Committee on Medical Education.

After the discussion of **Federal Government's Emergency Maternal and Infant Care**, the following resolutions were adopted:

Whereas, The Executive Board of the American Academy of Pediatrics meeting in full executive session at the Palmer House in Chicago on November 6, 1943, is in complete sympathy with the objective that the wives and infants of the service men should receive the best quality of obstetric and pediatric care during the present emergency, and

Whereas, The Children's Bureau has inaugurated plans and regulations to carry out the intent of Congress to provide a high type of medical care for the wives and children of our men in the Armed Services, and

Whereas, The present administrative regulations as set up by the Children's Bureau have, in the application of the program, revealed certain weaknesses which seriously interfere with securing such high type of medical care for wives and infants of service men,

Be It Resolved, That in order to attain the high quality of medical service to which the wives and children of service men are entitled, it is the sense of this Board that the Children's Bureau should call, forthwith, a conference of official representatives of the service men, together with official representatives of the professions actually rendering this service; namely, the American Medical Association, the American Hospital Association, the U. S. Public Health Service, the American Association of Obstetricians and Gynecologists, and the American Academy of Pediatrics. The purpose of the initial and future conferences to be the solution of the common problems which have arisen and will continue to arise until a method based on American democratic principles shall be established and utilized, and

Further Be It Resolved, That copies of this resolution shall be sent to the central offices of the above-named and other interested organizations.

Meeting Adjourned.

Report of Region I

As I render my final report after nine years of service to the Academy, as state, associate regional, and regional chairman, I first wish to express my deep personal appreciation to all the individual Fellows, the Regional Meeting Committee members, the state and province chairmen, and the national officers, who have labored so willingly and faithfully with me to see that the Academy objectives of better child health and better pediatricians progressed steadily in Region I through the years. Not once, in all these years, has any Fellow of the Academy failed to do cheerfully and well any task asked of him, and this splendid, whole-hearted devotion to the work of the Academy on the part of every Fellow in this region has made serving you in these chairmanships both a privilege and a pleasure. The scientific presentations and the personal good fellowship shown by all of our Fellows at our regional meetings have resulted in a splendid all-round Esprit de Corps contribution to the advancement of better child health in this part of the country. In our opinion, the Fellows of Region I are outstanding, as a group of physicians, in their devotion to the cause of child health and in their very real willingness to serve the Academy.

There are twenty-one medical schools in this region, each with a pediatric staff. Some years ago, a departure from the original routine of holding regional meetings mainly in Boston, New York, and Philadelphia was made in the direction of holding every second regional meeting in other cities where medical schools were

located. The response and hard work of these medical school pediatric departments and local Fellowships has been nothing short of amazing. Splendid regional meetings were put on in Rochester, Baltimore, Washington, and New Haven, and several more were in the two-year process of building at Buffalo, Baltimore, and Pittsburgh when the war brought a temporary hiatus. Each of these meetings, we feel, has immeasurably strengthened the Academy and child health in that part of our region, and this policy has seemed definitely to aid the Academy in its proper position as the main source of pediatric leadership in our country.

As in 1942, our main concern in Region I has been that of maintaining wartime child health at the best possible levels as the major responsibility of the Fellows of the Academy. The handicaps of personnel and other factors have been great, coupled with the great increase in the birth rate; but the health statistics throughout the region have shown that child health, generally, has more than held its own under these adverse conditions—an astonishing result of the good will and teamwork of all concerned with child health in this country and a great tribute to our Fellows and physicians generally and their co-workers in the health and welfare fields, a very real contribution toward winning the war and the peace to come. The region held a state chairmen's meeting on October 23 in New York, N. Y., on Child Health Wartime Problems, with national officers and Children's Bureau staff participating.

The particular situation in each of the states and provinces of Region I has been again ascertained by a 1943 questionnaire sent out to all state and province chairmen, as to the status of the main wartime child health needs in each state, such as the Control of Communicable Diseases, Child Care Centers, Nutrition Programs, and Essential Medical Care for Children, particularly in military and industrial areas. In general, the child health important needs were being reasonably well cared for, and in many instances real advances have been made as in peacetime. In a moderate number of localities, pediatric care of the children of war workers and men in service needs increased facilities, and definite steps are being taken to strengthen most of these to provide for these situations.

The special program (through the Children's Bureau and state health departments) of obstetric and pediatric care for the wives and children of men in military service is developing very well in this region, but the child care center programs, in spite of large federal funds and planning, seems to be meeting many difficulties in many locations. The reasons for these difficulties have not yet become completely clear, but the fact that these centers are developed largely through educational agencies rather than health agencies seems to us to be one of the main causes of the lack of successful progress in some cases. Considerable controversy and discussions are going on in Washington and elsewhere, and undoubtedly the situation will be clarified soon. It is to be hoped that progress will come soon, as the need undoubtedly exists, but many more children seem to have been cared for by friends, relatives, and neighbors than in the child care centers up to the present time.

Because of the lack of a national meeting of the Academy this year, a few of the highlights should be quoted from some of the state chairmen's reports of the region for the information of interested Fellows.

Dr. Tisdall, Ontario, reports that the prevention and control of communicable diseases has been unusually effective this year. He cites the fact that in a recent year not a single case of diphtheria developed in Toronto, a city of more than three-fourths of a million population. The National Nutrition Program in Canada (which Dr. Tisdall directed) has had good results, and the Canadian Medical

Association and Life Insurance Companies of Canada have initiated the second nutrition program in April, 1943.

Dr. Goldbloom, of Quebec, states that Fellows in Quebec have been participating actively in the general nutrition program.

Dr. Rogers, of New Hampshire, reports that the Academy Fellows carry on their usual close integration with all state and local health and welfare agencies; that standards for day care centers have been set up in a legislative bill and signed by the governor; that in some rural places good medical care for children is somewhat limited; that all work on the New Hampshire children's aid program is done or directed by Academy Fellows, except in the field of psychiatry. He also states that he was a member of the state's Surplus Food Commission but that that commission is about to expire, as even in New Hampshire there are now no surplus foods.

Dr. Johnson in Vermont reports that all the wartime child health programs are doing well, as does Dr. Webster in Maine.

Dr. Sisson reports from Massachusetts that the constructive integration of Fellows with the State Bureau of Child Hygiene and other agencies goes forward; that the stimulation of New England child health generally, through the New England Pediatric Society (Dr. Sisson is the present president of this society) as to the solution of wartime child health problems continues of particular interest is the Dental and Nutritional Program in that state, where excellent research and educational work is going on.

Dr. Sisson raises the very pertinent question as to how you tell in a state whether nutritional programs are effective.

Dr. Utter reports from Rhode Island that child health conditions are reasonably satisfactory throughout the state, with the exception of two industrial areas near Providence; that considering war conditions many expected health emergencies have not materialized; that the Child Health Relations Committee has made a good deal of progress on the care of premature infants and the use of vitamin K routinely on all newborn infants and are attempting to promote more universal breast feeding, not only because of the health advantages to mother and infant, but as a means of saving the time of the doctors in this war emergency.

Dr. Stringfield in Connecticut reports that pediatric care in Connecticut is still on a high standard—that the outstanding problems at present are day child care centers for working mothers, juvenile delinquency, and the administration of maternal and infant care for wives and children of service men. The day care centers have difficulty retaining help. Efforts are being made throughout the state to stem the tide of juvenile delinquency with but little success to date. The study of the program for maternal and infant care of the wives and children of service men by the Public Health Committee of the State Medical Society has resulted in the following resolution: "It is the opinion of this Committee that when Congress reconvenes proper efforts be made to change the law to the effect that obstetric and pediatric care be granted to wives and children of service men on the basis of need; that the funds awarded be paid to the patients with the provision that they be used for the purpose designated." If this change could be made, they feel sure that their obstetricians and pediatricians in Connecticut would be glad to cooperate, as it would leave them free to maintain for these mothers and infants the same physician-patient relationship that they have always enjoyed with their private patients.

Dr. Beaven reports from Northern New York that child health conditions are good with the exception of two areas—one around Tonawanda and another around Rome, where good medical care for children is being supplemented by the State Department of Health staff. There has also finally been formed in the New York

State Medical Society a Child Health Committee, which is directed by two leading Fellows of the Academy. This committee is actively studying the programs of the soldiers' children, child care centers, etc., and are making real progress through the State Department Education and the State Medical Society in the matter of establishing in the schools a good course for the study of health, with the aid of three consultants, two of whom are Fellows of the Academy (Dr. Silverman and Dr. Beaven). These Fellows are very active in this promising field of health education.

Dr. Martin, of Metropolitan New York, also reports as to the formation of the new Child Welfare Committee of the State Medical Society (Dr. Martin is chairman of this Committee). He states they are cooperating with the State Department of Health on the program of maternity and infant care for families of military men. He further reports that New York, under the leadership of Governor Dewey, is planning, on a state basis, a complete program of medical care of children of working mothers in child care centers and the provision of good medical care for children in military and industrial areas and similar activities, with an expected total budget, largely from New York State's funds, of 15 million dollars for these purposes. Governor Dewey feels strongly that states who are able should provide for their own needs and not constantly look to the Federal Government to solve health problems that they could more effectively solve in the states.

Our chairman for New Jersey, Dr. Harrold Murray, has been very active and reports that most wartime child health needs and health services are being well cared for in New Jersey. He has formed a State Academy Committee which is assisting the State Department of Health in the prevention and control of the infectious diarrhea of the newborn, in hospitals.

Dr. Murray is a member of the State Child Care Committee of the community war services and deputy chief of Emergency Medical Services in Essex County. Other Fellows serve on various local defense councils in the matter of child health. He states that the Child Care Committee of the state community services is engaged in a very effective program and is being supported by the Academy Fellowship. New Jersey Fellows held a meeting on October 22 in New York on child health wartime problems and invited the Fellows and child health and welfare workers within 100 miles to attend.

Dr. Lyon and Dr. Gilmartin, for Pennsylvania, under many handicaps, have formed a State Committee of Fellows and report reasonably good conditions throughout the state as to wartime child health needs. They report that, even in busy wartime, many of the Fellows, in spite of heavy pediatric burdens, are helping by making child health speeches before groups selected by the Committee on Cooperation with Nongovernmental Agencies. Their State Committee and Fellowship held a conference on these problems in conjunction with the meeting of the Pennsylvania State Medical Society on Oct. 7, 1943, in Philadelphia, where further plans will be made based on the findings of the Academy Fellowship in Pennsylvania at that meeting.

The child health problems, particularly in the heavy industrial cities of Delaware are very difficult, but Dr. Handy and the Delaware Fellowship, working with the state health and welfare agencies, are doing their best to meet these needs which, in some areas, need a great deal further supplementary aid.

Dr. Smith, of Maryland, calls attention to the prevalence of meningococcus meningitis, particularly in Baltimore, with its connection with overcrowded housing conditions in wartime. He further states that the Maryland State Health Department has appointed a committee to modernize the rules and regulations concerning communicable diseases, to facilitate their control. Child health conferences have been set up wherever feasible in close association with new child

day care centers, as the state has a number of problems connected with care of children in the many industrial and military areas where enormous increased wartime population has occurred. He states that there is much to be desired in the quantity and quality of medical care for children in some military and industrial areas and that an interesting effort is being made jointly in Middle River, Baltimore County, by the local medical society and the local health department to solve the medical care situation. The school health programs, due to wartime pressures and shortage of personnel, have had to be considerably curtailed in many places.

The District of Columbia, under the chairmanship of Dr. Donnally, has surpassed all of the states and provinces of Region I in its splendid program for meeting wartime child health needs. This is fortunate, because Washington, in many respects has necessarily encountered in this war greater health and welfare problems than almost any other city. The Academy has formed a strong Wartime Committee for Child Health Needs of the American Academy of Pediatrics and is doing a superlative job on each of the wartime needs, working in close conjunction with the health and welfare departments of the District of Columbia. They have added pertussis vaccine inoculations to the public health program. One of the Academy Fellows, Dr. Anderson, represents the committee on the Defense Council and acts as the liaison officer in making plans for the evacuation of children and other emergencies concerning children. Dr. Ellen Oppenheimer, Chief of the Maternal and Child Welfare Division, and Dr. Hugh J. Davis, Chief of Child Hygiene of the District of Columbia Health Department, are members of the committee and are liaison members in the fields of child health and welfare. The committee has aided Dr. Oppenheimer in setting up regulations for day nurseries and day child care centers, but wartime conditions are such as make them difficult of efficient enforcement.

Dr. Margaret Nicholson, a Fellow of the Academy, represents the Academy on the Committee of Nutrition, Civilian Council of Defense. They have concentrated on giving free luncheons to needy school children. Because of meat and egg shortages, they have stimulated poultry raising by well-to-do women in the District of Columbia. Dr. Donnally states there is no apparent lack of good medical care for children in the District of Columbia in spite of the tremendous housing problems.

The committee is also assisting the health department in their efforts to have Congress pass a bill for an adequate mental hygiene program for the District of Columbia which is very much needed and is also working closely with the director of School Medical Inspection Services as to school health needs, particularly the needs of the school children who have defective vision and defective hearing. This well-rounded program, under the handicaps of wartime conditions, reflects great credit on our Washington Fellowship.

These reports show a great deal of faithful work by many of the Fellows in the states and provinces under very difficult conditions and deserve our highest praise. These contributions to the wartime effort should be a source of great pride to all members of the Academy.

So far, in this report, we have discussed child health in Region I in the past and present. What about child health in Region I in the future? At the present time it has become apparent that we shall win this war in all human probability. Nations which have been following vicious leaders with wicked ideas are beginning to collapse one by one. While the struggle is still intense, we are bound to begin to think of everything, including child health, in the light of postwar conditions. Those of us who participated in the last war fully realize we lost the

peace by waiting until the war was over to build the foundations of peace. Therefore, the foundations of peace and progress in all branches of civilization, including better child health, must be laid while we are still at war.

The American Academy of Pediatrics, which is the chief reservoir of pediatric knowledge in these United States, should now, right in the middle of our struggles to meet child health wartime problems, face forward and study and plan with other child health workers the better child health of the postwar period. Great and pressing dangers challenge every phase of our former American Way of Life, and we should apply every bit of wisdom and experience we have gleaned in past years to the fashioning of a better child health world in the postwar period to come.

Some of us in the American Academy of Pediatrics have labored through the years, through conferences and various other methods, to develop cooperative child health plans and programs on a truly democratic basis. It has seemed to us that this method is the very essence of permanency in the working relationship of our Academy (and physicians generally) with all other groups of health and welfare workers. It now seems to us that the most important thing we can do at this juncture is to present for discussion our several ideas as to how we can best go on building better child health in our American democracy. May I, therefore, be forgiven, for presenting in this report, as my final contribution as chairman of Region I, some observations based on many years of experience in child health building in my own state and the region generally, with the hope that these thoughts may have some usefulness in the planning of our present and postwar children's health programs. The vital question is—"Just how shall we build child health in our American democracy?"

All of us who are engaged in building better child health in our American Democracy should band together and work together on an equal plane of endeavor in accordance with the true principles of American democracy.

In this platitude (if you mean by a platitude a high plateau of clear thinking on the level) is bound up the future of child health in America, and in better child health in these United States is bound up the future of our American democracy. The better world of tomorrow must be built by the children of today.

To prove this statement, we must answer three questions: First, What is a definition of modern child health? Second, Who are the child health builders? And third, How can we band together and work together in accordance with the principles of our American democracy?

The modern concept of child health is that of a child who is physically, mentally, and spiritually healthy. We have long known that a child must be physically healthy; in recent decades we have been finding out that a child must be mentally healthy; and the crystal-clear lesson of the present world struggle to preserve civilization is that a child must be spiritually healthy. There are some among us who would call this last vital essential moral or ethical health, but most of us (including Col. Eddie Rickenbacker) who are old-fashioned Americans call it Christian idealism, as we remember this country was founded as a Christian country. Even our coins read "In God We Trust." Some very sincere advocates of materialistic solutions seemingly would wish to have it now read: "In Man-Made, Collective-Planned, Economic Social Security We Trust." We must first foster the spiritual health of Christian ideals and goodwill to all mankind in our children's hearts. Without these ideals any man-made security may become a red tape mass of economic slavery. Without these ideals deep in our children's hearts we will lose the postwar peace, as ideals are essential to any world-wide lasting peace. Because of their lack in our enemies, this war came into being.

Having thus defined our conception of child health, the answer to the second question is simple. The child health builders are those groups who foster these various components of child health and aid parents in this building process.

Among the chief physical health builders are physicians (particularly our pediatricians), and our co-workers with children, the nurses, dentists, pharmacists, hospital workers, and workers in health departments and other kinds of child health agencies.

Building mental child health are pediatricians, educators, psychiatrists, psychologists, parent-teacher associations, and many other groups.

Building spiritual child health are the clergy and many affiliated religious and semireligious organizations, a truly impressive army of child health builders.

It is interesting to note that in 1859, eighty-four years ago, the first college health department was established in Amherst College, and Dr. Hitchcock created for it the concept of complete health with the teamwork of physicians, educators, and clergy as key workers to build the physical, mental, and spiritual health of the student—an old-fashioned but sound pattern for we modern child health builders.

The answer to the third question as to how we child health builders can band together and work together is not too difficult if we are all very careful to observe the true principles of an American democracy.

The basic principles of American democracy, which grew out of our forefathers' town meetings, were simple and consisted of: (1) working together for the public good on the level, on the square, on an equal plane of endeavor and opportunity, when delegation of power was necessary; (2) coming into being of elective representative government.

We child health builders can band together and work together splendidly if we will divest ourselves of all unnecessary trappings and any "delusions of grandeur" and faithfully observe these principles. We physicians need to lay aside some of our scientific superiorities; educators could become more like students; health and welfare officials of government and nongovernmental agencies could divest themselves of some official attitudes; the clergy could become less dogmatic. All of our child health co-workers could strive to get down to a common level of child health endeavor. On this common level we can accomplish much for child health provided that truly official representatives of all other child health groups are present and are given true equality of action. If we observe the true representative principles of our democracy and avoid the pitfalls of camouflaged advisory hand-picked "Yes men" committees, etc., we can together, build child health solidly and permanently, without sowing the seeds of eventual disintegration. We can do it if each of us has the goodwill to make the necessary sacrifices. I have every faith that we will do it as good Americans.

Having thus defined modern child health and specified the child health builders, with some American democratic ideas as to teamwork, we restate our high plateau of thought:

> "All of us who are engaged in building better child health in our American democracy should band together and work together on an equal plane of endeavor in accordance with the true principles of American democracy."

To paraphrase that great American, Abraham Lincoln, we should do this: "in order that better child health of the people, by the people, and for the people shall not perish from the earth."

Respectfully submitted,

STANLEY NICHOLS, Chairman

Report of Region III

Activity in Region III so far as meetings, state chairmen's reports, and committee reports have been virtually at a standstill during the past year. Fifteen members have been elected to membership, and three names are being submitted for action at this meeting of the Executive Board.

No request has been made for reports from state chairmen. It was felt that they were already overworked and that this was one burden which they could be spared. Unquestionably many of the activities in which the Academy is interested and for which the ground work was laid previously continues to be carried out in the various states.

One matter, however, has come up in Region III which should be presented to the Board for its consideration. The Nebraska Pediatric Society, through the Academy's state chairman, Dr. Henske, has forwarded a communication urging that national or regional meetings of the Academy be held. The fear is expressed that unless this is done members may lose interest in the Academy. Furthermore, the Nebraska group points out that other medical organizations have been holding regional and national meetings and that regional meetings in particular have been encouraged.

Following receipt of this communication a letter of inquiry was sent to each state chairman in Region III asking for an expression of opinion. Replies were received from all of the state chairmen except Dr. Kennedy, who was on vacation and could not be reached. Five state chairmen favored a regional meeting, and nine were opposed. One State Chairman pointed out that there would be a meeting of the American Medical Association in Chicago in June and that it would be difficult for him to attend any other meetings besides this one. Other reasons against holding either a regional meeting or a national meeting at the present time which were most frequently referred to had to do with difficulties in planning and giving a program by men already busy beyond their capacity, difficulties of transportation, hotel accommodations, etc. Those in favor felt that while there were difficulties, they were not insurmountable and that some sort of a suitable program could undoubtedly be arranged.

The Michigan state chairman felt that it was especially important at this time that a meeting be held and that the economics and future of pediatric practice be emphasized in the program. He felt that the pediatricians at home had a definite responsibility for the pediatricians in service to see that pediatric practice was not too much under governmental domination when these men return from their war duties. Region III believes this matter is one of considerable importance and recommends that it again receive the attention of the Board.

Respectfully submitted,

LEE FORREST HILL, M.D., Chairman
GEORGE F. MUNNS, M.D., Associate Chairman

Report of the Special Committee on Rheumatic Fever

Members of this committee attended a conference on rheumatic fever as Washington, D. C., Oct. 5 to 7, 1943, under the direction of the Children's Bureau, Drs. Gibson and McCulloch being also members of the Medical Advisory Committee on Services for Crippled Children, and Dr. Martin, the chairman of the committee, as representative of the American Academy of Pediatrics.

The purpose of the conference was to receive reports from all the states which are conducting programs for the care of children with rheumatic fever under the Social Security Act, Title V, Part 2, otherwise known as Crippled Children's Services. These programs have been inaugurated since the Act was created in

1939 so as to include rheumatic children in the group eligible to receive aid. This conference is the first to be held since that time and the first to consider exclusively rheumatic children as distinct from other types of crippled children. Many of the state directors of crippled children's services, together with cardiologists, pediatricians, public health nurses, and other professional aids, attended the conference. In addition, there were others representing many national and general organizations concerned with the problem of rheumatic children who attended. There were also specially invited guests, including representatives of the medical personnel of the Selective Service Bureau, the Army, and the Navy. Also your two members, together with Dr. T. Duckett Jones and Dr. Louise F. Galvin, on the Medical Advisory Committee attended and represented the medical group concerned with this problem.

A second purpose of the conference was to study the overall problem of rheumatic fever and heart disease in the population in all its aspects. The scope of the conference from this standpoint may be indicated from the following list of principal subjects which were discussed:

New Information on the Incidence of Rheumatic Fever
Case Finding
Diagnostic Clinic Services
Institutional Care of Children with Active Rheumatic Infection
Care of the Child with Active Rheumatic Infection in His Home or a Foster Home
Follow-Up Care (when the child no longer has active rheumatic infection)
New Methods of Therapy
General Administration of State Programs and Coordination of Community Resources
Further Development of Programs for Children with Rheumatic Fever

Finally, the conference was held to give consideration to a proposed plan to establish a national foundation to study this disease from the public health standpoint and also other phases, both clinical and investigative. This proposal is based on the apparent need for caring for such a major disease among children and young adults.

Your committee was created originally for an entirely different purpose, to cooperate with the Metropolitan Life Insurance Company of New York in preparation, publication, and distribution of a booklet for physicians on the general problem of rheumatic fever and heart disease. This function was fulfilled and the booklet is now available. By direction of the Executive Board, the committee was continued indefinitely to give further consideration to the development of a program for the control of rheumatic fever with power to study the whole field and return such findings as seem evident and important for the Academy to consider. The findings at the conference in Washington seem important enough to make this report.

First, the Children's Bureau program administered through the several states, fourteen in number, is well established, and it seems evident that in the near future many or all the states will have such programs. It, therefore, becomes of importance from a national standpoint. As fast as personnel becomes available, the program will be expanded and extended through the use of Federal, state, and local funds, using personnel of all levels. For this reason, the Academy will be faced with the question of deciding whether it will take an active part in this development or will stand passively by and see the work fall into other groups. Also, whether the Academy will act in an advisory capacity, serving when requested or will become one of the leading groups in the development. It is obvious that development will involve many other collateral activities of pediatric

interest with which the Academy concerns itself through other committees; for example, school health, summer camps, contact infections, medical and nursing education, legislation, hospitals, etc. An idea can be gained of the ramification of the problem into other fields of Academy interest from the suggestions which were made at the conference that school health examinations are far from satisfactory as a means of case finding for rheumatic fever and heart disease and might be discarded for a more accurate teacher-nurse classroom inspection and other more direct and satisfactory methods.

At this time the Executive Board and members of the Academy should be reminded that it was at a regional meeting of the Academy in Rochester, N. Y., in November, 1938, that at the request of Dr. Kaiser, a resolution was adopted suggesting to the Children's Bureau to consider heart disease in children a crippling condition. This recommendation gave special impetus to the idea that children with rheumatic fever and heart disease should be eligible for services under the crippled children's programs (see pamphlet, State Programs for Care of Children with Rheumatic Fever, Title V, Part 2, Children's Bureau, 1943).

Second, it is obvious that well-trained personnel is not now available in adequate number for any of the groups concerned and that not only will such personnel need to be made available, but special training must be created and offered to make that personnel available in the form of refresher courses, postgraduate courses for physicians, nurses, social workers, etc. Already the problem is being worked out by other groups, and the pediatric group is much concerned. It is also pointed out that the education of the general public and the medical profession at large, especially the local practicing physician, is a necessary part of the program, and at least part of this responsibility rests on the pediatric group.

It was pointed out that while rheumatic fever is primarily a disease of childhood and young adults and that only the end results in the form of chronic valvular heart disease are important in the mid- and late adult periods, most of the investigations, the information available, and the clinical care of rheumatic fever are still in the hands of specialists in internal medicine and general practitioners, and in general, pediatricians fall into the latter group so far as any real responsibility in the problem is concerned.

Third, if a national foundation is established either as a separate organization or as part of the American Heart Association or some other already existing organization, then a strong impetus will be given to the Children's Bureau program. Again the Academy will be called on to decide what part it will play in this. Rheumatic fever, like tuberculosis, is primarily a medical problem and, while much assistance and cooperation is desired and necessary from other groups, it must remain within the medical field. It is, therefore, a responsibility of the medical profession and a challenge to that group. It would seem advisable for the Academy to accept this responsibility in some degree. Two members already represent the Academy unofficially by their presence and inclusion on the Committee on Rheumatic Fever of the American Heart Association, Drs. Dunham and McCulloch. This committee was formed also in 1939 to cooperate with the Children's Bureau and to give consideration to the same problems.

The following suggestions are made as to how the Academy may act at this time:

1. The various state chairmen, committees, and individual members can concern themselves with the activities within their own states, serving in as close relationship as possible with the state directors of crippled children's services. For example, the Academy members can work actively for the establishment of cordial relations with the general practitioners within the state. Wherever possible, members can serve in either an advisory capacity or may actually be members of the services. This is particularly true in those states where pediatricians

have either special training or interests in rheumatic fever and heart disease. Provided teaching centers for postgraduate physicians or nurses are located within the states, then much of this highly specialized and very necessary work can be done by members of the Academy. Activities can be undertaken in connection with either state or local medical societies or other organizations. The matter of the education of the public and lay organizations would be a field of proper interest. Since the general idea of the program is to place the burden of care of these children on the general or special practitioner in the state, this relationship of clinic crippled children's services and doctor must be cultivated and worked out.

2. Wherever children's hospitals, clinics, or other such organizations exist which would be concerned in a general program, the relationship of the hospitals to the Children's Bureau and to the state Crippled Children's Services should be maintained. Many of these hospitals should be an actual part of the program, providing both hospital beds and clinic services for diagnosis and also care for those who are ill. Wherever convalescent or sanatorial institutions exist, these are most important and are an essential part of a state program, and the necessary number of beds in these institutions should be made available for rheumatic children. It is this type of care which is badly needed, and the reports from the various state directors indicate clearly a need for more beds of this type for borderline and Class I rheumatic children. Further information concerning these hospitals, clinics, and convalescent homes needs to be accumulated. A directory list of such institutions is available from the American Heart Association.

3. The Academy, as a national group, has a special responsibility to maintain an overall, active interest in and an indirect control of the program. Having played such a principal part in the initiation of the program, this interest must be maintained. Otherwise the control may drop into other less qualified groups and a great opportunity lost.

4. From all reports it is obvious that large numbers of soldiers will be discharged from the military service, either rejected because of doubtful or proved rheumatic fever and heart disease, or after having suffered from rheumatic fever after induction, either as a recurrence or from an initial attack. Already this is happening and the problem of the proper care of these individuals has presented itself. Whether this should be done through the Veterans' Administration or by the special care of doctors through the established centers for rheumatic fever control must be decided soon. While many of these individuals will be above the age of 21, many of them will not and the longer the war lasts the more the number below 21 will increase. While this group may not fall within the range of Academy activity, it will undoubtedly be a part of the problem presented to the various state services. And it is an essential part of the overall problem of rheumatic fever and heart disease.

5. In case it is deemed advisable to establish a national foundation for rheumatic fever, then the Academy must be prepared to share in the establishment and direction of such a foundation. Whether this organization should be made within and a part of the American Heart Association can be determined. It is suggested that mutual cooperative planning should be done by both groups.

6. It is not foreseen that the Academy will be called on for any financial assistance in this activity, but professional help, advice, and assistance of every kind is really needed.

7. It is requested that the present committee be made permanent.

Respectfully submitted,

Dr. Alexander T. Martin, Chairman
Dr. Stanley Gibson
Dr. Hugh McCulloch

Treasurer's Report

Statement of Receipts and Disbursements

July 1, 1943, to Oct. 31, 1943

Balance in checking account, July 1, 1943			$ 3,679.11
Balance in savings account, Initiation fees			8,018.08
Balance in savings account, International Congress			507.53
			$12,204.72
Receipts			
Dues		$23,397.00	
Initiation fees		500.00	
Interest earned		345.00	
Pamphlets			
Child Health Record	$ 145.00		
Immunization Procedures	66.30		
Vitamins	5.00	216.30	
Subscription—Men in Service		418.33	$24,876.63
			$37,081.35
Disbursements			
Bank charge and exchange		$ 61.24	
Certificates and mounting		26.76	
Executive board		12.00	
Miscellaneous		34.21	
Office supplies and equipment		29.49	
Postage		226.19	
Publicity			
Refunds—Initiation fees			
Rent		400.00	
Salaries			
Secretary	$2,500.00		
Assistant Secretary	200.00		
Stenographer	650.01		
Office	388.75	3,738.76	
Stationery and printing		98.76	
Subscriptions		6,836.73	
Telephone and telegrams		118.19	
Travel expense—Secretary		124.94	
Treasurer's bond		62.50	
Expense of:			
Regions	$ 873.97		
States	36.12		
Committees	155.00	1,065.09	
Pamphlets			
Child Health Record	$ 14.85		
Immunization Procedures	7.56		
Vitamins	.57	22.98	12,857.84
Balance, Oct. 31, 1943			$24,223.51
Balance in checking account, Oct. 31, 1943			15,197.90
Balance in savings account, Initiation fees			8,518.08
Balance in savings account, International Congress			507.53
			$24,223.51

The Pediatrician and the War

The following two letters in regard to milk and shoes for children in reply to the action of the Executive Committee at its meeting in November have been received by the Academy:

WAR FOOD ADMINISTRATION
FOOD DISTRIBUTION ADMINISTRATION
Washington, D. C.

November 18, 1943

Dr. Clifford G. Grulee
Secretary-Treasurer
American Academy of Pediatrics
1850 Gilpin Street
Denver, Colorado

Dear Dr. Grulee:

I acknowledge receipt of your letter of November 10 with reference to the meeting of the Executive Board of the American Academy of Pediatrics, and the copy of the resolution passed by the Executive Board.

The Food Distribution Administration recognizes the seriousness of the problem of supplying milk to classes of civilians who must have it regularly as a part of their diet. The shortage of fluid milk and of some other dairy products caused the War Food Administration to issue FDO-79. This order aims to control fluid milk sales and to encourage and help the fluid milk industry to the nation provide milk for priority classes of consumers as nearly as possible in the amounts needed to satisfy their nutritional requirements without the necessity of formal rationing by the Office of Price Administration. FDO-79 establishes priority classes of milk users. The order permits and encourages market agents to arrange with milk distributors to give special consideration to the nutritional needs of babies, pregnant women, growing children, hospitals, and invalids insofar as available supplies of milk permit.

As the market agents in the various milk markets perfect their administration of the order and strengthen their working arrangements with the industry, it is intended that more and more attention will be given to providing milk for the special priority classes of civilian consumers. Recommendations to market agents as to the quantities of milk that should go to the various types of consumers are based, insofar as possible, on the recommendations of the Committee on Civilian Nutrition of the National Research Council.

I thank you for your expression of interest and concern about these priority groups receiving the fluid milk they need to meet their nutritional requirements. I want you to know that careful consideration is being given the problems involved, and work is being done to see that adequate supplies of milk go to these nutritionally needy groups.

Yours very truly,

(Signed) Ralf Nugent
Assistant Chief
Civilian Food Requirements Branch

WAR PRODUCTION BOARD

Washington, D. C.
November 18, 1943

Dr. Clifford G. Grulee
American Academy of Pediatrics
636 Church Street
Evanston, Illinois

Dear Dr. Grulee:

Mr. Stephenson has asked me to answer your letter of November 8, 1943, together with a copy of your Executive Board's suggestion as to shoes for children, particularly under 10 years of age.

I know you will be interested to learn that many of us concerned with shoe production and distribution here in Washington, have spent most of this week considering the problem. Very frankly it is quite obvious that an increase in the number of ration coupons for children won't help the situation materially until we are certain that we have enough children's shoes to honor such an increase. The principal problem is to get more children's shoes of the various types and kinds that are greatly in demand. I am not at liberty to tell you what has transpired in these deliberations but I believe it is not out of order for me to state that the matter has our immediate and serious consideration and that steps are being taken that should help the situation.

If by any chance you know of specific instances where a physician has difficulty in securing a pair of shoes that is required for some one who is crippled, maimed or deformed, and where the shoes cannot come out of a retailer's stock but must be made up on special order to exact measurements, I would appreciate it if you would call the instance to my attention, giving me the name of the retailer and the name of the shoe manufacturer with whom the shoe retailer's order has been placed.

We recognize the exceptional hardship resulting from failure to secure such shoes that must be made to order and the War Production Board has given each instance, that we are aware of, special attention. Obviously we cannot do this in the case of the ordinary corrective orthopedic or specialty shoe which can be secured from retail stocks.

To take care of these latter cases is a part of the program to improve the whole children's shoe situation.

Very truly yours,

(Signed) Henry M. Spelman, Jr.
Henry M. Spelman, Jr., Chief
Leather Branch
Apparel, Textiles and Leather Products Division
Office of Civilian Requirements

Since our last report, the following Fellows of the Academy have entered service:

Army

Dr. Clinton Hollister, Santa Barbara, Calif. (Captain)
Dr. Harry E. Baldock, Charleston, W. Va. (Captain)
Dr. Paul N. Morrow, Omaha, Neb. (Captain)
Dr. Barnett P. Briggs, Little Rock, Ark. (Captain)
Dr. Robert H. Detwiler, Washington, D. C. (Captain)
Dr. Ralph E. Netzley, Pasadena, Calif. (Captain)

Dr. Samuel Schwartz, Washington, D. C. (Lieutenant)
Dr. I. M. Epstein, El Paso, Texas (Major)
Dr. Wm. B. Nevius, East Orange, N. J. (Captain)
Dr. Morris Y. Krosnick, New Haven, Conn. (Captain)
Dr. Herman B. Lander, Chicago, Illinois (Captain)

Navy

Dr. Burtis B. Breese, Rochester, N. Y. (Rank unknown)
Dr. Albert S. Harden, Jr., Maplewood, N. J. (Lieutenant)
Dr. R. S. McKean, Boise, Idaho (Lieutenant)
Dr. John A. Lichty, Jr., Rochester, N. Y. (Lieutenant)
Dr. Albert U. Peacock, Hartford, Conn. (Lieutenant)

Public Health Service

Carl Zelson, New York, N. Y. (Passed Assistant Surgeon)
Emmett E. Sappington, San Francisco, Calif. (Senior Surgeon)

Dr. George B. Kryder, Glendale, Calif., and Dr. Charles R. Barr, Philadelphia, Pa., have recently been discharged from service.

News and Notes

The American Board of Pediatrics has decided to reopen *Group I*, which requires that an applicant shall have been specializing in pediatrics for ten years or more, until *July 1, 1944.* After this date, this group will be abolished and all applicants will be required to fulfill the minimum requirements of three years of hospital training, two years of which must be pediatric.

The following dates have been set for examinations to be given to candidates by the American Board of Pediatrics:

Written examination, locally under a monitor, Feb. 4, 1944.

Oral examination, Philadelphia, Pa., March 25 and 26, 1944, San Francisco, Calif., May 6 and 7, 1944.

It has been officially announced that beginning Jan. 1, 1944, Dr. Stanley Gibson will be Physician in Chief and Dr. John A. Bigler, Assistant Physician in Chief and Medical Director, of the Children's Memorial Hospital, 707 W. Fullerton Ave., Chicago, Ill.

News has been received of the death in November of Dr. Roy P. Forbes, Denver, Colo., Dr. Charles W. Martin, Woodemere, Long Island, N. Y., Dr. F. D. Wilson, Norfolk, Va., and Dr. Harry R. Carson, Phoenix, Ariz.

Dr. William E. Ladd of Harvard University will deliver the twelfth annual series of the Benjamin Knox Rachford Lectureships at the University of Cincinnati on Tuesday evening, January 18, and on Wednesday evening, January 19, 1944, at 8:15 P.M. in the auditorium of the Children's Hospital Clinic and Research Building. The subjects of his lectures will be "Surgical Manifestations of Congenital Malformations of the Alimentary Tract" and "Experiences with Esophageal Atresia and Tracheo-Esophageal Fistulae."

Announcement is made that the Directory of Medical Specialists is now to be published by the A. N. Marquis Company, Chicago, publishers of *Who's Who in America.* Previous editions have been published for the Advisory Board for Medical Specialties by the Columbia University Press, New York, N. Y.

It is planned not to issue the next edition before 1945, because of the war, but the A. N. Marquis Company will publish a supplemental list of all those who have been certified by the American Boards since the last (1942) edition of the Directory, totaling about 3,600. This will be distributed at cost, and monthly or bi-

monthly bulletins listing successful candidates for certification at examinations during the additional interim before the next edition are to be issued as a subscribers' service.

Dr. Paul Titus, Pittsburgh, of the American Board of Obstetrics and Gynecology will continue as the Directing Editor, and Dr. J. Stewart Rodman, Philadelphia, of the American Board of Surgery, continues as Associate Editor. The Editorial Board will be composed, as before, of the Secretaries of the fifteen American Boards.

Communications should be addressed to the Directing Editor, Directory of Medical Specialists, 919 N. Michigan Ave., Chicago (11), Ill.

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